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SUBJECT.

The Cholesterol Content of Human Blood Under Pathological Conditions.

by

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The Cholesterol Content of Human Blood Under Pathological Conditions.

Introduction.

The lipoid substances have acquired so much significance in physiology and pathology in recent years that those investigators, who have devoted much time to an intimate study of the subject are inclined to ascribe to them a most important rôle in the animal economy. To quote Aschoff (1) "The doctrine of the undivided sway of protein as the supporter of life has been rudely shaken, and numerous and weighty examples are cited to demonstrate the great importance of the lipoids."

A specially interesting and important member of this group is Cholesterol, not only because of its wide distribution in the body, but also because of its ability to form ester-like combinations with the fatty acids, which are almost as frequently met with in tissues undergoing fatty degeneration as the glycerol esters themselves; while in addition, it plays a very important part in the economy of the organism. And it is with cholesterol that we are here concerned.

The present work comprises an investigation of the cholesterol content of the blood in various morbid conditions, and has been undertaken with the object of ascertaining how far blood cholesterol determinations might be of value in the diagnosis and prognosis of disease, while at the same time an attempt has been made to throw some further light on cholesterol metabolism.

Determinations of cholesterol have been made on the blood of 12 normal individuals and of 92 patients suffering from various diseases. The cases examined may be subdivided into seven groups, thus,

1. Normal cases.

2. Pregnancy.

3. Typhoid fever.

4. Cholelithiasis.

5. Cases associated with Glycosuria.

6. Genito-urinary conditions
   (a) Prostatic enlargements, benign & malignant.
   (b) Renal, urethral & vesical conditions.

7 Blood diseases
   (a) Anaemias, primary & secondary.
   (b) Conditions associated with Splenomegaly.

Some interesting and suggestive results have been obtained, but before proceeding with the account of the author's work, a brief description will be given of the known chemical and morphological characters of cholesterol and of its relations to physiology and pathology.

CHOLESTEROL - its chemical and morphological characters.

Introduction.

Since cholesterol was discovered by Conradi in 1775 and analysed by Chevreul in 1815, it has been found to be widely distributed in the animal, and in isomeric forms in the vegetable kingdom. It is found in small quantities in all protoplasmic structures, in bile, blood, sebum and similar oily secretions of the skin, and is an especially abundant constituent of the white substance of the brain and of the medullary sheath of the nerve.

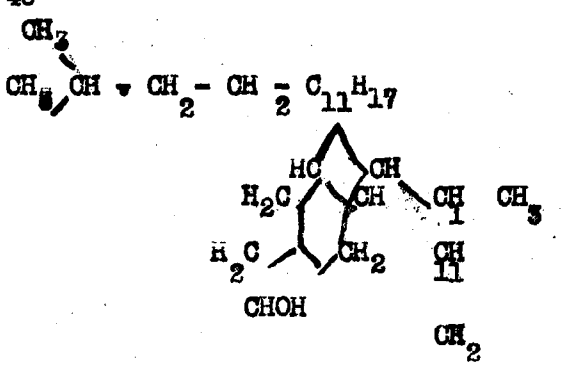
The fact that it also occurs in isomeric forms in the vegetable kingdom as the so-called phytosterols, makes it highly probable that it plays an important part in the economy of all living substances.

In addition to true cholesterol there also occur in human beings and mammals saturated derivatives of it, containing two additional hydrogen atoms, which are dextrorotatory, as opposed to cholesterol which is laevorotatory. These are found in the excretions of the body, as Isocholesterol in lanoline and as Coprosterol in the faeces of human beings and carnivora.

For our knowledge of the Chemical Composition of cholesterol we are indebted to the extensive and thorough researches of Windaus.(2)

According to this worker cholesterol has the formula

$C_{27}H_{46}O$, thus



The structure of $C_{11}H_{17}$ has still to be determined. It is thus seen to be a simple, unsaturated, monatomic, secondary alcohol, the hydroxyl group being placed in a hydrated ring, between two methylene groups. It contains one unsaturated bond and an isoamyl group, and possesses the characters of a complicated terpene.

Cholesterol possesses the power of forming crystalline addition products with the fatty acids, these taking the place of water of crystallisation. This "water of crystallisation" can be removed by heat or by treatment with alcohol and the alkali carbonates. It also forms simple and colloidal solutions with the fatty acids, neutral fats, soaps, especially the soaps of Tauro- and Glyco-cholic acids.

These have to be distinguished from the true esters which are saponified with difficulty and are less easily soluble in alcohol than free cholesterol. Until recently there was no exact method of differentiating between free and combined cholesterol. A great advance in this direction was made by Windaus (2) (1909) with the discovery of the Digitonin method. When cholesterol, in alcoholic solution, is treated with an alcoholic solution of Digitonin it

forms a complex compound,

Digitonin Cholesteride, which is precipitated as a fine crystalline powder. This is formed from a molecule of cholesterol and a molecule of digitonin, thus -

$C_{27}\ H_{46}\ O + C_{55}\ H_{94}\ O_{28} = C_{82}\ H_{140}\ O_{29}$

(Cholesterol) (Digitonin) (Digitonin-Cholesteride).

This addition product is insoluble in water, Acetone and ether, is soluble with difficulty in 95% alcohol, is more easily soluble in boiling alcohol, methyl alcohol, glacial acetic acid and pyridine. Free cholesterol alone combines with digitonin, the ester has first to be saponified. By washing with a mixture of alcohol and ether the cholesterol esters go into solution, leaving the insoluble Digitonin-Cholesteride behind.

Two colour reactions are made use of in the detection and quantitative estimation (colorimetric) of cholesterol, viz.

1. The Liebermann-Burchard reaction.

When to a chloroform solution of cholesterol (5 c.c.) 2 c.c. of Acetic Antydride and 0.1 c.c. of concentrated sulphuric acid are added a sequence of brilliant colours is obtained, viz. vivid pink, blue and dark green. In cholesterol solutions of low concentration only the green stage of the reaction can be seen.

2. The Salkowski reaction.

When to a solution of cholesterol in chloroform an equal volume of concentrated sulphuric acid is added and the two are well mixed by shaking, the chloroform rises to the top as a red coloured layer, while the subjacent sulphuric acid shows a well marked green fluorescence. On decanting the chloroform layer and adding water to it, it becomes colourless; the colour is regained on adding concentrated sulphuric acid.

Morphological Characters.

Adami and Aschoff (3) (1906) were the first to present us with a detailed morphological study of cholesterol.

Virchow in 1855 described what he termed "Myelin forms". He recognised myelin as, if not a single substance identical with the essential constituent of the medulla of nerves, at least, a class of substances which chemically were closely allied thereto.

A very characteristic property of a large number of myelin bodies is that of double refraction. If a fresh frozen section, or some of the expressed juice of the suprarenal, which is rich in myelin, be taken, what under the ordinary microscope appear to be minute fatty globules are seen in part to exhibit double refraction under polarised light. Between the crossed Nicol's prisms each little globule exhibits a black cross with four highly illuminated, bright and colourless intervening sectors.

These doubly refracting globules are "fluid spherocrystals". Lehmann's obvervations have shown that there exist substances which, when heated, pass into an intermediate state. From being solid they become fluid, but still, under polarised light, they are seen to maintain the characteristic crystalline feature of being doubly refracting. Heat to a further degree and the fluid becomes perfectly isotropic, without a sign of double refraction. In this intermediate phase we deal with crystalline fluids, and the individual crystals are fluid crystals, capable of being distorted by slight pressure.

The property of double refraction possessed by myelin was first observed by Mettenheimer in 1858, rediscovered by Apathy for nerve myelin in 1890, by Müller and Schmidt in 1898 for sputum myelin and again, independently, by Kaiserling and Orgler for suprarenal myelin in 1902.

(4)

After Kaiserling and Orgler (1902) had demonstrated the physiological occurrence of doubly refracting crystals in the cortex of the suprarenals and in the thymus, and their pathological occurrence in tumour cells, numerous publications appeared drawing attention to their occurrence in various other situations. The following list is taken from Aschoff.(4)

Cortex of suprarenals	Kaiserling and Orgler.
Atheromatous arteries	" "
Amyloid kidneys	Kaiserling, Orgler, Löhleim, Stoerk.
Chronic nephritis	" " " "
Lymphatics of the kidney	Löhlein
Thymus	Kaiserling and Orgler.
Sputum	Schmidt and Müller
Lymphatics of the Lungs.	Schultze
Tumours	Kaiserling and Orgler
Puerperal uterus	Munk
Epithelium of gall-bladder	Aschoff.
Lymphatics of mucous membrane of gall-bladder	Aschoff
Lutein cells	Kaiserling and Orgler
Xanthoma	Stoerk, Pick, Kammer
Choroid Plexus	Pick.
Pyosalpinx	Pick
Pyometra	Pick
Actinomycosis	Schlagenhaufer, Merkel.
Mesenteric cysts	White
Chronic mastitis	White
Tabes Mesenterica	White

and this by no means completes the list.

F.W. Beneke showed so long ago as 1862 that cholesterol played the chief rôle in the formation of myelin forms.

The researches of Panzer (1907)[5] and Adami and Aschoff (1906)[3] have demonstrated that the property of double refraction possessed by myelin forms is due to cholesterol esters. Panzer succeeded in isolating a cholesterol ester from pathological kidneys which were rich in doubly refracting material. Adami and Aschoff were able to synthesise cholesterol oleate by melting together Oleic Acid and cholesterol and the substance thus obtained seemed to be identical with the doubly refracting material found in the intima of atheromatous aortae.

Adami and Aschoff have demonstrated that soaps, especially the ammonium soaps, possess the property of double refraction and that mixtures of fats and fatty acids with cholesterol esters are doubly refracting.

In 1908, White[6] questioned whether Adami and Aschoff had really been dealing with cholesterol esters or only with mixtures of cholesterol and the fatty acids.

Craven Moore (1907)[7] went further still and denied the existence of true cholesterol esters in the organs, at least under physiological conditions, while Klotz (1909)[8] in an article on "The Large White or Soapy Kidney" attempted to show that soaps, and especially the oleates of sodium and Potassium, and not cholesterol esters were responsible for the phenomenon of double refraction.

It was with the object of clearing up this dispute that Windaus (1910)[9], at the request of Aschoff, examined some normal and pathological, fatty kidneys and determined the per-centage of cholesterol and cholesterol esters in both.

His figures are given below:-

I. Normal kidneys, weighing 280 grams contained

free cholesterol 0.26%

combined " 0.012%

II. Normal kidneys, weighing 238 grams, contained

free cholesterol 0.22%, and
combined " 0.030%

Normal kidneys, therefore, contain very little combined cholesterol.

III. Amyloid kidneys, containing but little doubly refracting material were found to have

free cholesterol 0.27%
combined cholesterol 0.090%

IV. Amyloid kidneys, containing abundance of doubly refracting material, gave on analysis -

free cholesterol 0.32%
Combined cholesterol 0.55%

V. Amyloid kidneys, containing abundance of doubly refracting material, gave on analysis -

free cholesterol 0.33%
combined cholesterol 0.65%

The above experiments show that normal and pathological kidneys do not differ much in their contents of free cholesterol, but the amount of combined cholesterol is very much increased in pathological kidneys, especially so in those containing abundant doubly refracting material.

Windaus (1910) was also able to isolate the cholesterol esters in pure condition from these kidneys and found that they were composed of two fractions, which he showed to be cholesterol palmitate and cholesterol oleate. These esters were handed over to Aschoff, who found that they behaved both in the polarising microscope and in relation to stains in exactly the same manner as the doubly refracting

substances which Aschoff had found in pathological kidneys.

These investigations proved conclusively that the doubly refracting droplets found in pathological, fatty kidneys were composed of mixtures of cholesterol oleate and cholesterol palmitate. The assumption of Craven Moore and White that they were addition products of cholesterol and the fatty acids was thus demonstrated to be incorrect.

Windaus (1910) further investigated other organs containing doubly refracting substances to find out if they yielded similar results. He carried out investigations on normal and atheromatous aortae.

His results are given below:-

Experiment I.

Normal aorta, weighing 57 grams, gave on analysis

Free Cholesterol	0.119%
Combined "	0.047%

Experiment II.

Normal aorta, weighing 31 grams, gave on analysis -

Free Cholesterol	0.103%
Combined "	0.032%

Normal aortae are thus seen to contain very little combined cholesterol.

Experiment III.

Atheromatous aorta, weighing 78 grams, gave on analysis -

Free Cholesterol	0.741%
Combined "	1.053%

Experiment IV.

Atheromatous aorta, weighing 64 grams, gave on analysis -

Free Cholesterol	0.673%
Combined "	0.792%

The above experiments give results which are in accordance with the previous findings. They also show that in atheromatous aortae there is a great increase in the cholesterol esters, but the free cholesterol is also increased, in contra-distinction to amyloid kidneys which showed an increase in cholesterol esters alone.

In addition to occurring in the tissues as anisotropic globules and cylindrical myelin forms, the combinations of cholesterol and the fatty acids are also found as needle like crystals - Stewart (1915) (11)

Pure cholesterol also occurs in two forms, as the wellknown rhomboid crystals and, occasionally, as bunches of fine needles or prisms. The needles of cholesterol esters differ from those of pure cholesterol in that when heated to a temperature (30-70°C) they melt to form spherical globules, which, on cooling, show the phenomenon of anisotropism for a longer or shorter period. Adami (1910) (12) thinks it is possible that during life they are actually present in the tissues in this fluid crystalline state.

In tumours, Powell White has shown that the crystals present in and among the healthy living cells consist of cholesterol in combination with fatty acid, and that in formalin fixed material they may be found either as needles or as anisotropic globules. The plates and needles of pure cholesterol, on the other hand, are all extra cellular, and occur only in the necrotic parts.

Intracellular crystalline cholesterol, especially when present in any amount, is always associated, in paraffin sections, with a foamy appearance of the cytoplasm. This is well seen, under physiological conditions, in the cells of the adrenal cortex, especially the zona fasciculata and in the recent or fairly recent, corpus luteum. Under pathological conditions intracellular lipoid deposits occur chiefly in relation to subacute and chronic

inflammatory lesions, especially where there is retained pus or secretions rich in lipoid, e.g. subacute cholecystitis, pyosalpinx, pyonephrosis, mastitis, etc.; also in tumours, especially hypernephroma of the kidney, cholecsteotoma, and in the various forms of Xanthoma.

It is difficult to say whether the foamy appearance is due entirely to the cholesterol present, since, in these cases, it is always associated with neutral fats and other lipoid substances. The affected cells show up prominently in paraffin sections, because of their faintly staining finely granular cytoplasm and because of their well defined limiting membrane. The nuclei are small and darkly staining and are sometimes placed eccentrically.

In frozen sections stained with Nile blue sulphate the appearance varies in different cases. Cholesterol is usually present in the form of fine needle like crystals, unstained and doubly refracting, but occasionally as fluid crystals. The globules may be unstained or coloured pink or blue from association with other lipoids.

Stewart (1915)(11) found that when foamy cells were present in large numbers they showed up to the naked eye as opaque yellowish areas, similar in colour and appearance to the outer parts of the suprarenal cortex.

The extracellular deposits consist of pure cholesterol and the crystals present are usually of the rhombic or plate variety. In paraffin sections, deposits of plate cholesterol give rise to a very characteristic appearance, namely, that of elongated oval or cigar-shaped spaces, with sharply cut margins and devoid of

contents. They show great variation in size, from tiny clefts not exceeding 10 ~~inches~~ in length, to huge elongated spaces extending across the whole low power field of the microscope. (11) Stewart (1915) considers that "their appearance is so constant and characteristic that I think the term cholesterin clefts might suitably be employed to describe them". The clefts lie scattered about in all directions, but when subjected to pressure they tend to lie more or less parallel to the free surface.

Physiological Significance.

The physiological significance of cholesterol has been the subject of much controversy.

(13) Austin Flint (1862) published a series of experiments by which he attempted to show that cholesterol is always more abundant in the blood coming from the brain than in the blood of the general arterial system, or in the venous blood from other parts; that its quantity is hardly appreciable in venous blood from the paralysed side in hemiplegia, and that it is separated from the blood by the liver. He also stated that in case of serious structural disease of the liver accompanied by symptoms pointing to blood poisoning, cholesterol accumulates in the blood, constituting a condition which he named cholesterolaemia. He came to the conclusion that cholesterol is a product of metabolism of nervous tissues, that it is carried from the brain by means of the blood and excreted through the liver by means of the bile, and finally, that "we know of no function which it has to perform in the economy any more than urea or any other of the excrementitious principles of the urine".

Dorée and Gardner (1907-8)[14] state that "Flint's method of analysis are open to grave objection, and that he draws sweeping conclusions from differences so slight that, even had his method been capable of considerable accuracy, one would have hesitated to attribute much significance to the figures".

Some support, however, was lent to Flint's views by the experiments of Picot and Mueller. Picot (1872)[15] reported a fatal case of grave jaundice in which he found great increase in the cholesterol of the blood. Müller (1873)[16] injected cholesterol into the veins of dogs and produced a complete representation of the phenomena of "grave jaundice". Fels and Ritter (1876)[17] and Rywasch (1888)[17] obtained opposite results and established the view, since repeatedly confirmed, that cholesterol is nontoxic.

Hoppe Seyler believed that cholesterol was a cleavage product formed in the metabolic changes in the living cells and because of this was invariably found as a chemical constituent of both animal and vegetable cells. He also believed that it did not easily undergo decomposition in the animal organism and that it was excreted in the bile, that none of it was reabsorbed, but that it was purely an excretion product, passing out of the body with the faeces.

Flint showed correctly that cholesterol is found in the human faeces in the modified form of stercorine. This body was rediscovered by Bondzynski in 1896 and renamed by him coprosterol. He regarded it as a dihydro-cholesterol formed by bacterial reduction in the intestine. Müller (1900)[18] showed that on a milk diet, in which the putrefactive processes in the intestine are reduced to a minimum, the cholesterol of the body is excreted unchanged.

Dorée, Ellis, Fraser and Gardner (1908-1912)[19] have put forward

the following hypotheses with regard to the origin and destiny of cholesterol in the body.

(1) Cholesterol is a constant constituent of all cells, and, when these cells are broken down in the life process, the cholesterol is not excreted as a waste product, but is utilised in the formation of new cells.

(2) A function of the liver is to break up red blood corpuscles and excrete their cholesterol in the bile.

(3) After the bile has been poured into the intestine in the process of digestion, the cholesterol is reabsorbed, probably in the form of esters, along with the bile salts and carried by the blood to the various centres and tissues for re-incorporation into the constitution of new cells."

There is some wastage of cholesterol in the body, as not inconsiderable quantities are excreted through the skin. This wastage is probably made good from the cholesterol of the fedd. The food of carnivora is rich in cholesterol and it might be readily utilised. The food of herbivora, on the other hand, contains no cholesterol, but the closely related phytosterols, and one has to assume that the animal converts these into cholesterol.

The later work of Dorée, Ellis, Fraser and Gardner supports these hypotheses and seems to warrant the following conclusions.

(1) An increase in the cholesterol content of the blood and liver, directly proportional to an increased intake of cholesterol in the diet, occurs in animal feeding experiments, the kidney content not being affected.

(2) Where food is withheld (inanition) there occurs an increase in the cholesterol content of the blood, liver and kidneys.

(3) In the human subject a cholesterol balance can be established, that is, the ingested cholesterol can all be accounted for in the faeces, but the incidence of an acute infection with loss of weight disturbs this, yielding a positive balance in the faeces.

Gardner and Lander's (1913-14) results suggest that the organism is able to pick out and conserve cholesterol from a diet of an exceedingly low cholesterol content. These workers consider it highly improbable that cholesterol can be synthesised in the animal body, for the following reasons.

(a) Herbivora, whose food normally contains no cholesterol, do not excrete cholesterol in their faeces. What they do excrete when they are fed on grass is a cholesterol-like body - hippocoprosterol, $C_{27}H_{54}O_{56}$. This hippocoprosterol was shown by Dorée and Gardner (1907-08)[21] to be derived from the grass ingested, and the amount of it contained in the faeces varied directly with the amount of grass consumed. These observations further show that cholesterol cannot be regarded as a waste product, for although the bile of these animals contains an appreciable quantity of cholesterol, none of it is excreted.

(b) Dorée and Gardner (1908-09)[21] showed that cholesterol is excreted by rabbits when they are fed on it, and when administered with the food, about 50 per cent of it is absorbed.

(c) Ellis and Gardner (1908-09)[21] showed that in "the differentiation of the ovum into the complex aggregate of cells constituting the chick no formation of cholesterol takes place."

From the above it would appear that cholesterol is not synthesised in the body nor is it destroyed. Yet Dezani[22] and Lifschütz[23] are of the opinion that it is readily synthesised.

Lifschütz (1908)[23] believes that it is formed from oleic acid. He has actually succeeded in obtaining from oleic acid, carefully freed from all traces of cholesterol, by a process of oxidation with Potassium Permanganate in the presence of glacial acetic acid, a substance which gave the characteristic colour reactions of cholesterol. He concludes that oleic acid, in the process of oxidation, becomes partly converted into cholesterol, or if not into cholesterol at least into a very closely allied derivative of it. I shall have occasion to refer to this later.

Another point in favour of Lifschütz's hypothesis is the claim of Iscovesco (1912)[24] and Terroine (1914)[25] that the blood cholesterol is increased during the absorption of fat free from cholesterol. Bloor (1916)[26], however, has failed to confirm this.

Lifschütz (1914)[27] also thinks that cholesterol is broken down in the body and that it may be the source of the bile acids. An oxidation product - oxycholesterol, $C_{27} H_{46} O_2$ is known to occur in the blood and tissues of the body and it has also been prepared in vitro by the oxidation of cholesterol. While it is present in the blood in considerable quantities, only small amounts are found in the other organs and tissues, and in the liver it can scarcely be detected. Lifschütz showed that oxbile and the bile acids by a process of oxidation become converted into substances which give the colour reaction (with its characteristic spectrum) of oxycholesterol. This leads him to suggest that the bile acids are probably derived from the cleavage products of oxycholesterol.

Leaving the disputed question of the origin and destiny of cholesterol in the body we shall now turn to a consideration of its function. This, too, is but little understood.

(1) It is closely related to immunity and is said to stimulate the production of antibodies. Chauffard has demonstrated that serious infections are always accompanied by a marked hypo-hypocholesterolaemia, while Landau (25) and others have found that the suprarenal cortex showed a markedly low content of lipoid material in patients who died of infective conditions.

Observations made on the condition of the adrenals at post mortem examinations in the Leeds Pathological Department during the last few years strongly support this finding.

Immunisation processes, on the other hand, have been shown to be accompanied by an exceptionally high cholesterol content of the blood.

Barbary (29) has been applying in practice the points learned in recent research on lipoids in general and on cholesterol in particular.

According to this clinical worker the latter seems to stimulate the production of antibodies. By injecting cholesterol directly along with camphor, which he believes stimulates the production of cholesterol, the cholesterol content of the blood rapidly increases and the body repels or throws off infection and recuperates much earlier and more effectually than is otherwise the case. This has been Barbary's constant experience with the sick and severely wounded. In his hospital at Nice there have only been 4 deaths among the 767 wounded and 9 among the 797 sick during the last 21 months and the deaths among the wounded were explained by other reasons.

(2) Cholesterol has the power to act as an antihaemolytic agent against substances like saponin, tetanolysin and cobra venom.

Only free cholesterol has this antihaemolytic power, as was shown by Windaus (1909).[2] It probably acts as such by forming an ester like compound through the free hydroxyl group. Lecithin acts antagonistically in this respect, for it activates the lysin.

(3) Cholesterol is said to promote cell multiplication. Robertson and Burnett (1913)[30] have found that injections of cholesterol cause an increase in the rapidity of growth of tumour transplantations in rats.

An increase in the cholesterol content of the blood in pregnancy and a fall to normal during the puerperium have been observed by Hermann and Neumann (1911)[31] Chauffard, Laroche and Grigaut (1911)[32] and others.

Luden (1918-19)[33] believes that a high cholesterol content of the blood is an important factor in the etiology of malignant disease. Moreover, she has actually found that high blood cholesterol values were the rule in such cases.

(4) It plays a part in the metabolism of the fatty acids. During the absorption of cholesterol from the intestine large quantities of esters are formed. Iscovesco (1912)[24] and Terroine (1914)[25] claim that the blood cholesterol is increased during the absorption of fat free from cholesterol. Bloor (1916)[26] as already stated, has failed to confirm this.

Further evidence of the participation of cholesterol in fat metabolism is afforded by the fact that cholesterol bears a strikingly constant relation to the other blood lipoids. This is well shown by the recent investigations of Bloor (1916)[34]

on the partition of the lipoids in normal and pathological bloods including severe diabetic lipaemia.

Lastly we may mention the different organs that have been held responsible by various workers for the regulation of cholesterol metabolism and its elimination. (Quoted from Luden)(35)

(1)	Adrenals	(Rothschild, Sternberg and Landau)
(2)	Liver	(Rothschild, Weltmann, Anitschkow and Chalatow)
(3)	Spleen	(Aschoff, Landau, Rothschild, McMeans)
(4)	Ovary and Corpus Luteum	(McMeans)
(5)	Hypophysis	(Warthin)

Role of Cholesterol in Pathology.

This will be dealt with but very briefly here, as it will be considered again along with the discussion of my own cases.

The recognition of the occurrence of cholesterol under pathological conditions dates back to the time of its preparation from gall-stones.

Deposits of cholesterol esters occur pathologically at the sites of low-grade chronic inflammations, for example, amyloid kidneys, subacute and chronic parenchymatous nephritis, in chronically inflamed Fallopian tubes, in pneumonic exudates. They are also found in malignant tumours, in the cells of Xanthomas, in the retina, forming the white spots in Diabetes and Bright's Disease, in the arcus senilis of the cornea, etc.

Deposits of free cholesterol occur under conditions of slow cell destruction in areas where absorption is poor.

The solitary gall-stone is composed almost entirely of pure cholesterol.

Changes in the cholesterol content of blood in disease have been investigated by an number of observers, such as Grigaut, Iscovesco, Westen and Kent, Bacmeister and Henes, McNee, Bloor, and others.

The normal content of the blood serum is given as 0.15-0.18 gms. per 100 c.c. Free cholesterol is present in the corpuscles and plasma; cholesterol esters in the plasma alone. According to Bloor the average percentage of combined cholesterol is 33.5 of the total cholesterol in normal whole blood and 57.5 in normal plasma.

Changes in diseased conditions are both quantitative and qualitative. The cholesterol content of the blood is increased in Arteriosclerosis, chronic Bright's disease, Diabetes Mellitus, Xanthoma or Xanthelasma and always in pregnancy. It is decreased in almost all febrile diseases, severe anaemia, tuberculosis and cachetic conditions.

As to the qualitative changes some workers have found that in jaundice there is a great increase in the free cholesterol of the blood as compared with combined. In nephritis and carcinoma, too, Bloor (87) has obtained low values for esters in the plasma, while in pregnancy the values for cholesterol esters have been found to be high.

In Chronic Bright's disease Bacmeister (36) and Henes obtained values varying from 0.236 to 0.426 gms. per cent; In Eclampsia from 0.274 to 0.321 gms. per cent. In Chronic Uraemia the content was equally high. The values were independent of the amount of albumen in the urine. The more severe the condition, the more marked was the hypercholesterolaemia.

The interest in the increased cholesterol content of the blood in Nephritis and Eclampsia is enhanced when certain other manifestations of these conditions are considered.

Lauber and Adamük[37] have shown that the white spots which appear in the retina in early cases of nephritis consist of a deposit of cholesterol esters. These white retinal spots also appear in Eclampsia and are said to disappear when the cholesterol content of the blood returns to normal.

Marie and Laroche[38] have shown that the arcus senilis of the cornea, which is so often associated with vascular changes in old people, is a cholesterol ester infiltration of the cornea.

In Diabetes an increased cholesterol content of the blood was noted by Fischer[39] as early as 1903 - the value obtained by him in a case of severe diabetic lipaemia was 0.478 gms. per cent. While the increase is inconstant in moderate cases, it is very marked in severe cases. The retinal white spots which are sometimes seen in cases of Diabetes have been shown by von Noorden to disappear entirely as the condition improves with diet.

In all forms of chronic jaundice the cholesterol content of the blood is increased. McNee (1913-14)[40] states that in chronic hepatic disease, unassociated with jaundice, such as Cholelithiasis, no increase is found. This is contrary to the findings of Henes,[41] Bacmeister[36] and Henes, and others who believe that hypercholesterolaemia is an important aetiological factor in Cholelithiasis. Aschoff and Bacmeister[42] have shown that gall stones may be classified according to their composition as follows:

(1) Pure Cholesterol stones.

(2) Stratified cholesterol calcium stones.

(3) Cholesterol-pigment-calcium stones, which are of most frequent occurrence.

(4) Composite stones made up of cholesterol and a mantle of cholesterol and calcium.

(5) Bilirubin calcium stones; these are seldom found in the gallbladder but are usually found in the biliary passages of the liver itself.

(6) Calcium carbonate stones which are seldom met with.

Cholesterol is thus seen to play a very important rôle in the formation of gallstones.

In Xanthoma or Xanthelasma the presence of a hypercholesterolaemia is suggested by the fact that this condition sometimes occurs in the course of chronic nephritis, diabetes mellitus and jaundice. The cholesterol content of the blood in 2 cases examined by Apert, Pechery and Rouillard [43] was found to be 0.315 and 0.530 gm. per cent. The lemon yellow tumours in the skin, which are characteristic of the disease, have been found to be composed of interstitial and endothelial cells filled with doubly refracting fat globules.

In pregnancy we have a physiological hypercholesterolaemia. The increase was first observed by Hermann and Neumann (1911) [31] and was later confirmed by other workers.

In infective conditions such as Typhus, Pneumonia, Erysipelas and various forms of sepsis, low values have been obtained. The cholesterol content of the blood is said to vary inversely with the temperature. Baumeister and Henes (1913) [36] are of the opinion that the hypocholesterolaemia in febrile conditions is caused by the high temperature and its results. They found no

marked decrease in the cholesterol content of the blood in two cases of severe facial erysipelas in which the temperature did not exceed 98° F. These workers also found that the cholesterol content of the blood soon returns to normal if the fever has lasted only a short time. If, on the other hand, the fever has lasted for a long time, the cholesterol content of the blood rises above the normal value and continues high for some time.

In chronic tuberculosis the values obtained seemed to be determined by the general condition of the patient. The same applies to cases of malignant disease. Bäumeister and Henes (1913)(36) found a hypercholesterolaemia in the early stages of malignant disease, while in the late stages, where cachexia was a marked feature, low values were obtained.

In severe anaemia, and particularly in pernicious anaemia the cholesterol content of the blood is much reduced.

Bloor (1917)(44) found that the blood lipoids in anaemia were normal, or nearly so, as long as the per centage of corpuscles remained over 50 per cent of the normal value. When it fell below this level, low values for cholesterol and lecithin and high values for fat were obtained. He also found that the ratio lacithin to cholesterol was generally high in pernicious anaemia due to relatively low values for cholesterol, while in secondary anaemia the ratio was usually normal.

In view of the fact that cholesterol is an antihaemolytic agent and that low cholesterol values are a characteristic feature of the blood of severe anaemia, there has been a tendency on the part of some workers to connect the low cholesterol values with the pathogenesis of anaemia. This will be fully described when

the author's work on anaemic conditions is reviewed.

Since cholesterol is readily absorbed from the intestine its therapeutic use in anaemia has been advocated by German and Italian workers.

Reicher (1908)[45] found improvements in a number of cases of anaemia after feeding cholesterol. Klemperer (1908)[46], on the other hand, failed to obtain satisfactory results.

Pacini (1918)[47] working in America obtained good results by administering cholesterol in the form of lanoline, as an innunction to anaemic patients.

On the whole, the treatment does not appear to have given satisfactory results in the hands of other workers.

Experimental Work with Cholesterol under Pathological Conditions.

Ignatowski (1909)[48] in experiments on rabbits, by substituting animal for the normal vegetable food, was able to produce vascular lesions and changes in the liver and kidneys.

Stanakadowski (1909)[49] obtained similar results by using egg yolk.

Stuckey (1910)[50] in a series of experiments used meat juice, egg white, egg yolk and milk and found that egg yolk induced a remarkable ~~proliferation~~ intimal change of cellular proliferation with lipoid infiltration in the aorta, but that the other food stuffs caused very little change. As egg yolk differs from the above mentioned food stuffs in being rich in fat, feeding rabbits on animal and vegetable fats was tried but this failed to reproduce the lesions.

The clue to the constituent in egg yolk which was responsible for the changes was given by Anitschkow and Chalatow (1913).[51]

These workers investigated the appearance of the liver of rabbits fed on egg yolk and brain. They found that the Kupfer cells of the liver were laden with fat droplets which were doubly refracting, that is cholesterol esters. Cholesterol then, appeared to be the constituent in egg yolk which was responsible for the lesions. This was confirmed by feeding rabbits on cholesterol, when results were obtained similar to those described above, but greatly intensified.

The lesions produced in the vascular system are almost entirely limited to the intima. Microscopically the elastic fibres are seen to be separated into a net-work of fine fibrils in the meshes of which are large phagocytic cells with round nuclei, and much vacuolated protoplasm "foamy cells" in fact. When examined under the polarising microscope these cells are seen to be filled with doubly refracting fat droplets, that is cholesterol esters. Slight changes are also observed in the innermost layers of the media, the muscular fibres becoming separated from each other and somewhat irregularly arranged.

These changes more closely resemble those found in human atheroma than any other arterial lesion so far produced experimentally, and are quite different from the medial changes which have been brought about by injections of adrenalin or staphylococci.

How far the experimental lesions produced in the aorta of rabbits can be applied in solving the problem of arterial disease in man it is difficult to say. So far the changes have only been produced in rabbits, all experiments on carnivora having failed,

Man is accustomed to a mixed diet and it is perhaps possible that a too richly animal diet may be a contributing factor in the development of atheroma.

The relation of cholesterol to the growth of neoplasms has been studied in experimental carcinomas in rats. Robertson and Burnett (1913)[30] have shown that cholesterol, when injected directly into tumours, causes a marked acceleration both of the primary and of the metastatic growth. The acceleration is most evident in the pre-metastatic stage. Lecithin has the opposite effect. It diminishes the tendency to form metastases, retards the metastatic growth when it does occur and in some instances also retards the primary growth, the retardation being most evident in the metastatic stage.

Luden (1918-19)[35] found high blood cholesterol values in malignant disease and she is of the opinion that the c hypercholesterolaemia is not due to cell destruction; as evidence thereof she cites the fact that the blood cholesterol is reduced by radium treatment, although radium causes cell destruction, and considers that the increased content may be the result of disturbed cholesterol metabolism. This, she believes, may be an evidence of a subnormal rate of basal metabolism, since the high cholesterol values of myxoedema are reduced by the administration of thyroid extract, and this, we know, greatly increases the rate of basal metabolism.

Luden believes that the disturbance of cholesterol metabolism is revealed by the absence of changed cholesterol or cholesterol split products in the blood of a high percentage of cancer patients, since she failed to get a difference between the

cholesterol values obtained by the Bloor I and Bloor II methods. Such a difference was constantly found by her in normal bloods and in pathologic, but non-malignant bloods.

Radium treatment and thyroid extract have been found by Luden to reduce the cholesterol content of the blood and increase the amount of changed cholesterol in the blood. She attributes the beneficial effects of radium therapy to this change in the chemical composition of the blood. She further suggests that as thyroid extract affects the blood cholesterol values in a manner similar to that of radium, the administration of thyroid extract may be expected to improve the condition of patients suffering from carcinoma.

Method employed in the estimation of Cholesterol.

At present there are in use several methods, of which the following is a brief resumé.

Until 1909 the only method available for the estimation of cholesterol in the tissues and fluids of the body was by treatment with a selective solvent, such as acetone or ether, and collecting and weighing the crystallised cholesterol after evaporation of the solvent. This method was employed by Fischer (1903)[39], and by Dorée, Ellis, Fraser and Gardner (1907-1909).[19]

In 1909 Windaus[a] introduced his excellent gravimetric digitonin method.

Since 1910 a number of colorimetric methods have been introduced. Thus, Grigaut[53] in 1910 described a colorimetric method of estimating the cholesterol content of the blood, in which he made use of the Liebermann-Burchard colour reaction. Two years later Weston[54] described a procedure in which the Salkowski colour reaction was employed; and in 1913 Autenrieth and Funk[55] described a slight modification of the Grigaut technique, and adapted it to use with the Autenrieth - Königsberger colorimeter. This modification has been extensively employed. In addition to these, Bloor[56], Usonka[57], Gettler[58], Baker and others have employed colorimetric methods.

In the case of the gravimetric digitonin method for the estimation of total cholesterol, a preliminary saponification of the cholesterol esters is necessary, since only the free cholesterol is precipitated by digitonin. This is not necessary with the colorimetric method, since the cholesterol esters give the same colour reaction as cholesterol itself. This fact does not appear to have been recognised until quite recently, when it was pointed out by Bloor[59] in 1916, and the colorimetric estimation of cholesterol thus becomes further simplified. The gravimetric method, though highly accurate, is too laborious, especially when several determinations are to be made at the same time.

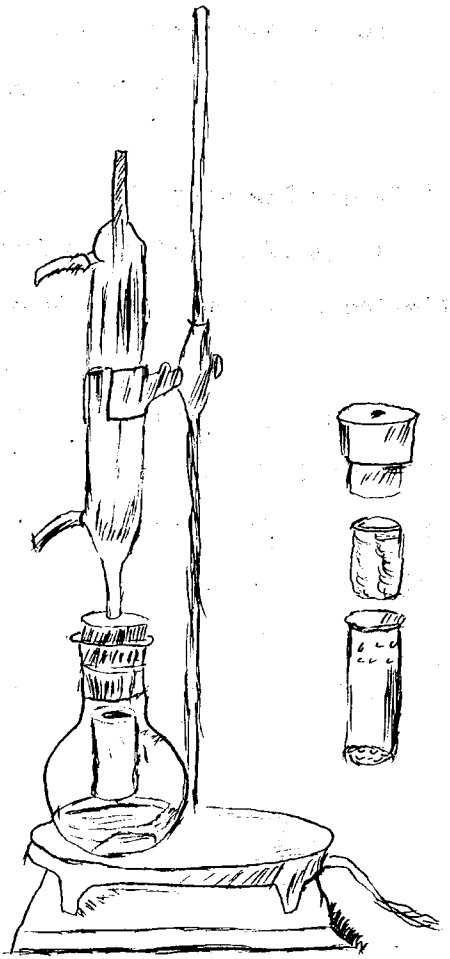
With regard to the colorimetric methods, one would infer from their multiplicity that they are not entirely satisfactory.

Bloor,[56] who has done a great deal of work on the blood lipoids, has suggested a method of extraction, which, though simple, and apparently complete, gives results by the modification finally carried out (second method), which are higher than those obtained by other methods, and are also rather irregular. Bloor himself admits that the results by his method are 7 to 30% higher than those obtained by Autenrieth and Funk and others, but he attributes them to a more complete extraction.

His method has been adversely criticised by Weston[60] and Mueller.[61] Weston failed to obtain valid results by Bloor's method, whereas the extraction methods of Autenrieth and Funk, Weston and Kent, Csonka, Gettler & Baker and Weston gave consistent results, added cholesterol being recovered quantitatively in each case.

Mueller[61] showed that Bloor's method gave high results but that the increase was not due to cholesterol itself. A possible cause for a part, at least, of this excess value may be found in the slight brownish colour invariably present in the chloroform solution of extracts prepared by the Bloor method. This brown colour is present no matter how carefully one avoids heating the residue after it is dry, and even when it is evaporated before a fan at room temperature, though Bloor claims that it is due to overheating.

Luden (1917)[62] obtained similar high findings with Bloor's second method. She ascribed them to a combination of bile acids and bile pigments present in the blood, as she was able to show that the Liebermann - Burchard reaction could be obtained with a mixture of cholesterol - free gallstone derivatives.



Cholesterol extraction Apparatus

(63)

Myers and Wardell (1918) have described a comparatively simple method of direct cholesterol extraction, which appears to yield reliable results. With this method they were able to recover added cholesterol quantitatively, while consistent duplicates were obtained as also satisfactory checks with the totally different and reliable Windaus' method.

This method appealed to the writer because of its simplicity; because the results obtained by it agreed with those obtained by other methods; and because of the small quantity (1 c.c.) of blood required. This has been an important consideration, as not infrequently a blood urea or blood sugar estimation had to be made on the same sample of blood.

A few slight modifications of Myers and Wardell's technique have been introduced in the course of the work, and the following is the detailed account of the method as found most reliable and satisfactory by me.

1 c.c. of blood, plasma or serum is pipetted into a porcelain crucible containing from 4 to 5 grams of plaster of Paris, and stirred and dried in a drying oven for three quarters of an hour at a temperature between 70 and 80°C. It is then emptied into a small extraction capsule (4 cm. long) and inserted into a short glass tube (2.5 x 6 cm.) in the bottom and sides of which are a number of small holes.

This is attached to a large cork on a small reflux condenser and the tube and cork inserted into the neck of a 150 c.c extraction flask, containing about 25 c.c. of chloroform. Extraction is continued for one hour on an electric hot plate, the chloroform made up to 20 c.c., filtered if necessary, and colorimetric estimation carried out as follows:-

5 c.c. of the chloroform extract are pipetted into a dry test tube; then 2 c.c. of Acetic Anhydride and 0.1 c.c. of concentrated sulphuric acid are added. After thorough mixing, the solution is placed in the dark for 15 minutes (at a temperature of 22° C) to allow the colour to develop, and is then compared with a standard cholesterol solution in chloroform, (0.4 mgms of cholesterol in 5 c.c. of chloroform), which had been similarly treated, in a Kober colorimeter, setting the standard at 12 m.m.

The procedure for the estimation of cholesterol in the red blood corpuscles is exactly similar, the corpuscles having first been freed from plasma by three successive washings with normal saline and subsequent centrifugalisation.

As to the modifications introduced into the original technique, it will be noted that it was found necessary to allow the extraction to continue for one hour, as it was quite incomplete at the end of 30 minutes as advised by Myers and Wardell. In the drying process, too, great care had to be exercised to prevent overheating, the most suitable temperature being found to be 70 - 80°C. When that was exceeded the Plaster of Paris assumed a brownish colour, and the sample, after extraction, gave a very weak colour reaction as compared with that obtained with the same sample of blood, in which overheating was avoided. This observation suggests that some of the cholesterol

must have been destroyed, or altered in such a manner that it no longer gives the Liebermann-Burchard reaction.

Instead of using aqueous Naphthol Green B as standard, as recommended by Myers and Wardell, it was found that the colours could be more easily matched when a solution of pure cholesterol in chloroform (0.4 mgm. of cholesterol in 5 c.c. of chloroform) was used as a standard.

The most suitable temperature for the development of the colour reaction was found to be 22°C. as pointed out by Bloor (1917) [64]. He showed that the blood cholesterol behaves differently from the standard cholesterol; it reacts more readily with the reagents, comes to its maximum sooner, and begins to fade sooner than the standard cholesterol. Values obtained at 22°C. are more nearly correct than those obtained at higher or lower temperatures. At lower temperatures the standard colour has not fully developed, while at higher temperatures the blood cholesterol has passed its maximum and has begun to fade.

The author's experience coincides with that of Myers and Wardell as to the absolute necessity of using perfectly anhydrous reagents in order to avoid weak colour reactions.

Using this method it was found that the samples of blood did not deteriorate with keeping, provided they were placed in the ice-chest, and they were therefore worked up at any convenient time.

In order to determine whether ingestion of food had any immediate effect on the cholesterol content of the blood, a patient was selected who was able to eat a hearty breakfast consisting of 2 eggs, bacon, bread and butter, and tea with cream. Blood was taken before breakfast, that is after a fast of 15 hours, and again 3 hours after breakfast.

Cholesterol per 100 c.c. of blood.

1. Fasting 0.261 grams.

2. 3 hours after breakfast 0.255 grams.

The claim of Dennis (1917)[65] that the ingestion of food, rich in lipoid material, has no immediate effect on the cholesterol content of the blood, has thus been substantiated and the blood samples were, accordingly, taken at any convenient hour.

Findings of the Present Investigation with a Discussion thereon.

As already stated in the introduction determinations of cholesterol were made on the blood of 104 persons including 12 normal individuals.

The results obtained in the normal cases are tabulated below.

I. Normal Cases

Case	Age	Sex	Cholesterol per cent.
1. A.S.	28	♀	0.191
2. J.C.	22	♀	0.155
3. T.W.	58	♂	0.164
4. C.M.	40	♀	0.160
5. B.A.W.	53	♀	0.180
6. R.C.	18	♂	0.156
7. H.W.	20	♂	0.148
8. M.M.	46	♂	0.153
9. A.T.	43	♂	0.191
10. W.B.	47	♀	0.164
11. R.O.	29	♂	0.133
12. A.T.	17	♂	0.150

The normal cholesterol content of the blood is seen, from the above, to vary between 0.191 per cent and 0.133 per cent, with an average of 0.161 per cent, values which are in agreement with those given by Chauffard, Laroche and Grigaut (1911)[32], whose figures are 0.150 to 0.180 per cent, and also with those given by other writers.

II Pregnancy and the Puerperium.

Bloods were examined in 4 cases of pregnancy and one case of puerperium. The results are tabulated below.

Case	Age	Age of pregnancy	Cholesterol in per cent	Remarks.
1. Mrs. O.	28	2 months	0.288	Wassermann positive.
2.Mrs. H.	26	5 "	0.183	Very anaemic
3.Mrs. A.	29	7 "	0.196	Anaemic
4.Mrs. C.	33	7 "	0.231	
5.Mrs.G.	21	4 months after delivery	0.170	

There is then, an increase in the cholesterol content of the blood in pregnancy, and after delivery the value returns to normal. This is in accordance with the findings of other workers.

Neumann and Hermann (1911-12)(31) were the first to draw attention to the hypercholesterolaemia of pregnancy. This was confirmed by Chauffard, Laroche and Grigaut (1911)(32) and others.
Hermann and Neumann also showed that there was a retention of lipoids during pregnancy and an elimination during the puerperium, the chief means of excretion being the milk, and that the hypercholesterolaemia passed off more quickly in women who suckled their infants. Cf. Case 5 above.

McNee (1913)(66) examined the bile of 4 pregnant women who died and found that there was a marked increase in the cholesterol content of the bile in pregnancy.

Landau (1913)(28) showed that the suprarenals shared in the retention of lipoids which occurred in pregnancy.

During pregnancy, then, not only is there an increase in the cholesterol content of the blood plasma, but the organs which are concerned with its storage, utilisation or excretion also show an increased content. This would seem to support the view expressed by Aschoff and Bacmeister (1909)(42) that a cholesterol diathesis is responsible for certain cases of gallstone formation, for gallstones are of more frequent occurrence among women, especially those who have borne children.

III Typhoid Fever.

All workers are agreed that fever reduces the cholesterol content of the blood. With the disappearance of the fever the cholesterol content of the blood rapidly increases. Typhoid fever is said to be an exception. Thus Chauffard, Richet and Grigaut (1911)(67) obtained high cholesterol values in the late stages of typhoid fever. McNee (1913-14)(40) and Small (1915)(68), in reviews of the literature on the subject, both mention typhoid fever as an exception to the hypocholesterolaemia which occurs in all other febrile conditions.

The author examined the blood in 4 cases of typhoid fever. The case histories are given in the appendix

The results are tabulated below (Table III).

Table III.

ase	Age	Sex	Day of illness	B. Typhosus isolated	Fever	Widal	Cholesterol in per cent.
. L.B.	17	♀	17th	+	+	+	0.100
		Convales-cent	41st		−		0.190
			59th		−		0.160
. F.H.	14	♂	14th		+	+	0.120
		Convales cent	40th		−		0.200
. X.	19	♀	21st		+	+	0.120
. Nurse D.	32	♀	60th Blood taken after death.	+		+	0.100

In these 4 cases there was a hypocholesterolaemia in the febrile stages of the illness, while at the commencement of convalescence a hypercholesterolaemia manifested itself, cf. cases 1 and 2.
As seen from case 1 the cholesterol content of the blood returned to normal towards the end of convalescence.
These results are contrary to the findings of previous workers, but they are quite in accord with what one would expect to find in an exhausting illness accompanied by high fever, lasting for several weeks.

The high values obtained by previous workers may be accounted for by the fact that they probably examined the blood in the early convalescent stage when a hypercholesterolaemia is present.

Conclusions.

I. In the febrile stage of 4 cases of typhoid fever a hypocholesterolaemia was found.

II. In 2 cases a hypercholesterolaemia was observed in the early stage of convalescence.

III. In one case examined the cholesterol content of the blood was found to have returned to normal.towards the end of convalescence.

IV. Cholelithiasis.

12 cases of cholelithiasis were examined and 2 cases which were clinically diagnosed as such, but subsequently proved to be other conditions, viz. malignant disease of the stomach and appendicitis.

A brief history of each case will be found in the appendix.

The results are given in Table IV.

Table IV.

Case	Age	Sex	Diagnosis	Cholesterol in per cent Before operation.	After Operation	Time after operation.
1.M.M.	61	♂	Cholelithiasis	0.193	0.127	7 days
2.J.J.F.	41	♂	"	0.230	0.215	4½ months
3.Mrs.E.	38	♀	"	0.147		
4.Mrs.N.	43	♀	"	0.168		
5.Mrs.C.	37	♀	"	0.198		
6.Mrs.M.J.C.	56	♀	"	0.289	0.100	9 days
					0.106	17 "
7.Mrs.B.W.	54	♀	"	0.263		
8.Miss P.	20	♀	"	0.228	0.140	7 "
9.B.I.	48	♀	"	0.186	0.131	7 "
10.Mrs.D.	59	♀	"	0.250		
11.Mrs.W.	47	♀	"	0.163		
12.Mrs.M.E.	63	♀	"	0.156		
13.Mrs. F.	65	♀	Circular neoplasm of jejunum and suppurative pylephlebitis	0.170		
14.S.G.	43	♂	Appendicitis	0.085		

Summary and Discussion of Results.

In the 12 cases of cholelithiasis examined 7 showed a hypercholesterolaemia while 5 gave normal values.

After operation the cholesterol content of the blood fell below normal, as seen in cases 1.6.8 and 9. In case 6 the blood cholesterol content 17 days after operation was still as low as 0.106 per cent. In case 2, 4½ months after operation, the cholesterol content of the blood was above normal (0.215%), yet it was below the value (0.230%) obtained prior to the operation.

The hypercholesterolaemia following operation may be attributed chiefly to the drainage of the biliary passages. The effects of the anaesthesia, the slight elevation of temperature almost invariably present after an operation, and, indeed, the disturbed metabolism consequent on operative shock must also be regarded as contributing factors.

It is to be noted that operation in conditions other than cholelithiasis lowers the cholesterol content of the blood, as will be seen later.

These results are not in agreement with those of Henes (1914),(41) who found that the hypercholesterolaemia of cholelithiasis persisted for "a considerable time after removal of the stones". He examined the blood in 7 cases, 3, 4, 5, 7, 19, 21 and 22 days after operation. In the 5 cases examined by me the cholesterol content of the blood was found to be much reduced 7, 9, 17, 8 and 7 days after operation, while in one case (case 2), 4½ months after operation, the cholesterol content of the blood, though above normal, was below the value found before operation. This discrepancy between my own findings and those of Henes may

depend on a difference in surgical technique as to post-operative drainage of the biliary passages. As Henes does not make specific comment on this point, I am unable to make any dogmatic statement.

Henes (41) claims that "conditions simulating cholelithiasis can be differentiated therefrom by cholesterol serum determinations. This particularly applies to differentiating duodenal ulcer from cholelithiasis".

This statement is too sweeping. While the majority of cases of cholelithiasis show a hypercholesterolaemia, this is not always the case. Thus it will be seen that five of the writer's cases gave a normal cholesterol content of the blood. This observation is in accordance with the findings of Rothschild and Rosenthal (1918) (69). These authors cite 12 cases in which the blood showed a normal cholesterol content, and yet, gallstones were found at operation. Their explanation of this group of cases is that at some previous period a hypercholesterolaemia was present, since the calculi found in the gallbladder are doubtless a relic of a former blood condition of high cholesterol content.

The presence of infection, empyema of the gallbladder, for example, will reduce the cholesterol content of the blood even in cholelithiasis. Then, too, in duodenal ulcer, while low cholesterol values are the rule, concomitant pathological conditions, such as arteriosclerosis, chronic nephritis, may cause a hypercholesterolaemia.

At the same time, when a very low value is obtained for the cholesterol content of the blood in a case of supposed cholelithiasis, it should make one suspect some other condition. Case 14 is an example in point. This patient was diagnosed as a case of cholelithiasis. The cholesterol content of the blood just before operation was 0.085 per cent. There was no fever at the time to

account for the low value. At operation the gallbladder and biliary passages were found to be perfectly normal, but there was an inflammatory condition of the appendix.

The relation of cholesterol to gallstone formation has been emphasized by many writers. Naunyn (1898)[70] claimed that cholesterol was an excretory product of the epithelium of the gallbladder and bile ducts.

Aschoff and Bacmeister (1909)[42], are of the opinion that when cholesterol is found in the epithelium of the gallbladder it is due to resorption from a saturated bile.

Chauffard and Bacmeister (1914)[71] have called attention to the relationship of hypercholesterolaemia to gall-stone formation. In pregnancy there is a physiological hypercholesterolaemia and it has been well established that gall-stone formation is more frequent in women who have borne children. Bacmeister and Henes (1913)[36] have shown in their work on a pregnant dog with a biliary fistula that there is a real retention of lipoids in pregnancy. With the birth of the young there is an excretion of the retained lipoids chiefly through the mammary secretion.

Rothschild (1914)[72] has shown that the cholesterol content of the blood and bile depends upon the type of food consumed by the organism. The complete cholesterol metabolism was outlined by Rothschild as follows:-

"There is no synthesis of cholesterol in the body. Our supply of lipoids is maintained by our food intake. Free cholesterol is esterised in the intestinal canal, absorbed by the lymphatics, delivered to the blood stream and then distributed to the body cells. With the breaking down of cells, as in general catabolic processes, it is again freed to the blood stream, carried

to the liver, where the endothelial cells possibly produce a de-esterization, excreted with the bile as free cholesterol, and again partially re-esterized and reabsorbed from the intestinal tract by means of the lymphatics".

Chalatow (1913)[73] has produced small concretions in the gall-bladders of rabbits by feeding large quantities of cholesterol, these stones consisting practically of pure cholesterol.

The importance of cholesterol as a factor in cholelithiasis has also been emphasized by De Langen (1916)[74]. His studies on the cholesterol content of the blood in Holland and the Dutch East Indies have shown that there is a marked differance between the Europeans and the natives of the Dutch East Indies in this respect. In the latter the cholesterol content of the blood is about half the European figure and that of the bile also is very low. In Japan the figures are midway between those in the Dutch East Indies and in Holland. De Langen was led to this research by noting the extreme rarity of gall stone trouble in the East Indies. When gall-stones are found, they are not the cholesterol stones of Europe, but are composed principally of a mixture of calcium and bilirubin.

Rothschild and Rosenthal (1916)[69] distinguish 2 groups of cases in cholelithiasis.

(1) Cases with a normal cholesterol content of the blood.

(2) Cases that are hypercholesterolaemic.

(a) Obstructive hypercholesterolaemia,

temporary (stone, stricture, new growth).

(b) Diathetic hypercholesterolaemia,

with obstruction
without obstruction { Intermittent
{ Permanent.

The obstructive hypercholesterolaemias are temporary, the cholesterol content of the blood returning to normal with the removal of the obstruction.

The diathetic group of cases are more or less continuously hypercholesterolaemic. After operation these patients remain free of symptoms for three months to one year, when the symptoms return. Even after removal of the obstruction the hypercholesterolaemia persists.

In cases without obstruction there are 2 groups, those with intermittent and those with permanent hypercholesterolaemia. As an example of the intermittent type Rothschild and Rosenthal cite the following case. A patient with gradually progressing hypercholesterolaemia develops and attack of cholelithiasis. The precipitation of the retained lipoids in the gall-bladder or bile ducts in the form of cholesterol stones, with or without subsequent explusion, automatically diminishes the cholesterol content of the blood. Because of the diathesis, however, the hypercholesterolaemia again increases until once more relieved by lipoid precipitation. The permanent hypercholesterolaemias are of similar nature, but in them the cholesterol content of the blood at no time returns to the normal value.

If we accept this classification, cases 3,4,9,11, and 12 belong to Group I. Their symptoms will probably never return unless the same physiologically or pathological conditions which originally caused the hypercholesterolaemia should return.

Cases 1,6,and 8, in all of whom the original hypercholesterolaemia was replaced by a marked hypercholesterolaemia after the operation, may provisionally be placed in Group II (a). The cholesterol content of the blood ought to be determined at a

later date before finally placing them in this group.
Case 2 belongs to the diathetic group, that is II (b).
4½ months after operation this patient is hypercholesterolaemic.

The remaining cases can not be classified as no blood cholesterol determinations were made after operation.

Rothschild and Rosenthal (1916)[69] recommend that the blood of every case of cholelithiasis should be examined before operation. In the presence of hypercholesterolaemia provision should be made for drainage of the bile, in order to deplete the body of the retained lipoids. After removal of the drainage tube the blood should again be examined and if the cholesterol content of the blood is high, the patient belongs to Group II (b). Further accumulation of cholesterol can be controlled by dietetic measures, since the cholesterol content of the blood depends on that of the food.

Conclusions.

I. While hypercholesterolaemia is the rule in cholelithiasis normal values are by no means uncommon.
II. The finding of a marked hypocholesterolaemia should make one question the diagnosis of cholelithiasis.
III. The statement made by Henes that conditions simulating cholelithiasis can be differentiated therefrom by serum cholesterol determinations must be accepted with considerable reservation.
IV. Systematic determinations of the cholesterol content of the blood before and after operation appeared to be of undoubted value in the prognosis and subsequent treatment of cases of cholelithiasis, as already pointed out by Rothschild and Rosenthal.

TABLE V.

Diabetes Mellitus. and "Renal Glycosuria"

ASE.	AGE.	SEX	CHOLESTEROL IN PER CENT.	SUGAR IN BLOOD.	DIAGNOSIS.
. g.g.	33	♂	0.260		Diabetes Mellitus.
. W.E.	31	♂	0.177	0.11	" "
. H.C.	47	♀	0.204	0.26	Diabetes M and Phthisis.
. R.W.	26	♂	0.380	0.35	
		19 days later	0.238	0.17	Diabetes Mellitus
		14 " "	0.188	0.15	
. A.G.	38	♀	0.190	0.098	Renal
				0.072	Glycosuria.

Group V.

Cases associated with Glycosuria.

5 such cases were examined, Brief histories and clinical findings are given in the appendix. The values obtained are recorded in Table V.

Discussion of Results.

Cases 1, 2, 3 and 4, are typical cases of Diabetes Mellitus while Case 5 appears to be a case of "Renal Glycosuria", since after protracted observation, both while in hospital and afterwards, there was marked glycosuria without hyperglycaemia. (For details see appendix).

As seen from the accompanying Table the chelesterol content of the blood varies, though not in direct proportion, with the sugar content of the blood. Thus, in Case 2, both the chelesterol and sugar content of the blood are within normal limits. In cases 1, 3 and 4, along with the hyperglycaemia there is also a hypercholesterolaemia. Moreover, in Case IV, with the decrease in the sugar content of the blood, there is seen to be a fall in the chelesterol content of the blood.

In Diabetes Mellitus an increased chelesterol content of the blood was noted by Fischer (39) so long ago as 1903, and was later confirmed by other workers. It is interesting to note that the white spots in the retina often met with in Diabetes and now known to be composed of Chelesterol esters, may disappear entirely as the general condition of the

patient improves with the diet.

A more marked hypercholesterolaemia may be found in the lipaemia of Diabetes, than in any other condition. (75) Joslin, Bloor, and Gray (1917) found that the cholesterol content of the blood in Diabetes gives valuable information regarding the general lipoid content. They state, "The increase in cholesterol is significant and suggestive, and seems, indeed, pathognomonic of the prolonged diabetic hyperlipaemia, since Bloor has found it lacking in the acute lipaemia of overfeeding which is characterised by an increase in the total fatty acid alone."

De Langen (1916), (74) in his studies of the cholesterol content of the blood in Holland and the Dutch East Indies, found that in the natives of the East Indies it was about half the European figure. Glycosuria is of rare occurence among them. Thus, ina group of 5,800 sick natives of the Islands there were only 5 cases of Diabetes Mellitus, while in a corresponding average group at the Groningen Hospital in Holland the year before, he had found 22 diabetics among 1,200 patients. In Japan, also, glycosuria is very rare, and it is so mild that, as a recent Japanese writer has said, it does not deserve the name of Diabetes.

De Langen was led to take up this research by noting the extreme rarity of Diabetes in the East Indies and Japan.

In view of the association of hyperglycaemia and hypercholesterolaemia in diabetes it is interesting to note that McCrudden and Sargent (1916 and 1918), (76) found that in progressive muscular dystrophy hypoglycaemia was associated

with hypocholesterolaemia. This apparently physiological relationship between glucose and cholesterol suggested that there might be a parallelism between the two substances in the blood in other conditions. McCrudden and Sargent [76] failed to find such a parallelism.

Conclusions.

(1) In two cases a hypercholesterolaemia was associated with a hyperglycaemia. In two other cases in which the sugar content of the blood was normal, a normal value was obtained for the cholesterol content of the blood.

(2) In one case in which several successive cholesterol and blood sugar determinations were made, the improvement in the patient's general condition under dietetic treatment was accompanied by a fall in the sugar and the cholesterol content of the blood.

(3) In conditions associated with Glycosuria there appears to be a parallelism between the cholesterol and sugar content of the blood.

TABLE Vl. (a) Cases of Obstruction due to Prostotic Enlargement.

CASE	AGE	SEX	CLINICAL DIAGNOSIS.	DATE WITH REGARD TO OPERATION	CHOLESTEROL IN PER CENT	UREA in mgms per 100ce	REMARKS.
1.B.W.	62	♂	Enlarged Prostate	1 day before operation.	0.215	25.2	Suprapubic prostatectomy; well.
2.J.H.	62	♂	" "	1 week before "	0.247	16.8.	Suprapubic prostatectomy ᴍ ᴍ Died. P.M. findings: Oedema of lungs, coronary atheroma, small gall stone in cystic duct. Old T.B. glands.
3.J.H.P.	70	♂	" "	1 day " "	0.089		Suprapubic cyctotomy; drainage. Died.
				4 days after "	0.074	25.2	P.M. findings: enlarged prostate, acute cystitis; acute ascending pyelonephritis. Perinephritic abscess.
4.C.Tr.	65	♂	" "	8 " before "	0.205	28	Suprapubic prostatectomy; well.
5.A.M.	62	♂	" "	17 " " "	0.300	16.8	Suprapubic prostatectomy; well.
6.R.S.	69	♂	" "	5 " " "	0.270	42	Suprapubic cystotomy. Died. P.M. findings: Carcinoma of prostate with metastases to aortic lymph glands. Multiple gall stones. Patchy thickening of mitral and tricuspid valves. Coronary atheroma.
7.S.T.	78	♂	" "		0.130	42	Refused operation.
8.R.H.	68	♂	Enlarged Prostate; Cystitis; urgemia.	32 " after "	0.227	16.8	Suprapubic cystotomy; improved.
9.J.S.	55	♂	Enlarged Prostate	4 " before "	0.133	39.2	Suprapubic cystotomy; attends as out patient.
10.A.W.	74	♂	Enlarged Prostate; vesical calculus	1 " " "	0.126	75	Suprapubic cystotomy; calculus removed. Died. P.M. findings: benign enlargement of prostate; small abscesses of kidneys. Coronary atheroma and general arteriosclerosis.
11.H.W.	68	♂	Enlarged Prostate	2 " after "	0.092	42	
				14 " " "	0.108	42	Suprapubic prostatectomy; well.
				28 " " "	0.104	25.2	
12.E.M.	70	♂	Enlarged Prostate; cystitis	1 " before "	0.103) 0.110) 0.106	79.5	Suprapubic cystotomy. Died. P.M. findings Benign enlargement of prostate; acute cystitis and urethritis; left pyelitis and right pyelonephritis; purulent Broncho-Pneumonia and abscess left lower lobe.
13.J.W.	71	♂	Enlarged Prostate;	4 " after "	0.173	40	Suprepubic prostatectomy; well.
14.J.Rh.	60	♂	" "	2 " before "	0.136	22.4	Suprapubic prostatectomy; well.
15.W.H.	78	♂	Enlarged Prostate Malignant bladder.		0.166	33.6	Considered inoperable.

TABLE VI (a) Continued.

Case.	Age.	Sex.	Clinical Diagnosis.	Date with regard to operation.	Per cent. Cholesterolin	Urea in Mgms.100/cc.	REMARKS.
16 D.F.	49	♂	Enlarged Prostate	3 days before operation.	0.354	30.8	Suprapubic cystotomy. Died P.M. findings: Benign enlargement of prostate; bladder and kidneys normal. Atheroma of aorta; pulmonary emphysema.
17 I.B.	51	♂	" "		0.196	16.8	No operation; discharged; well.
18 J.B.	68	♂	" "	Day of operation	0.109	75.6	Suprapubic cystotomy. Died.P.M. Findings: Benign.enlargement of prostate; acute cystitis; intense acute ascending pyelonephritis; aortic and coronary atheroma.
19 J.S.	80	♂	" "	1 day after "	0.140) Duplicate. 0.140)	39.2	Suprapubic cystotomy; drainage; relieved
				14 days " "	0.160	25.2	
20 J.W.	58	♂	" "	3 days before"	0.150	25.2	Suprapubic prostatectomy; well.
21 R.P.	67	♂	" "	5 days " "	0.230	33.6	Suprapubic cystotomy; inoperable carcinoma at base of bladder.
				8 days after	0.113	30.	
				28 " " "	0.176		
22 C.C.T	56	♂	" "	3 days before"	0.133	16.8	Suprapubic prostatectomy; well.
				12 " after "	0.093	30.8	
23. S.B.	66	♂	Malignant Prostate; Carcinoma of Stomach.		0.070	30.8	Died. P.M. Findings: Carcinoma of rectum, fistula to coil of ileum and bladder, pyelitis. Old T.B. lungs.

Group VI.

Genito-urinary Conditions.

(a) Prostatic enlargements - benign and malignant.

23 cases of prostatic enlargement were examined. The results are given in Table VI(a). The more important clinical details regarding the individual cases will be found in the appendix.

Summary and Discussion of Results.

Of these 23 cases determinations of cholesterol were made on the blood of 16 cases before operation, of 3 cases (3,21,22) both before and after operation, and of 4 others (8, 11, 13, 19) after operation only.

The results obtained in cases 3, 21 and 22 bear out the observation already made in connection with the cases of cholelithiasis, namely, that operation has the effect of lowering the cholesterol content of the blood, and that this rises again as the patient recuperates.

In 9 of the cases (1, 2, 4, 5, 6, 8, 16, 17, and 21) a hypercholesterolaemia was present; 6 cases (7, 9, 14, 15, 20 and 22) gave normal values and in 5 (3, 10, 12, 18, 23) the cholesterol content of the blood was low. With regard to cases 11, 13 and 19, in all of which the cholesterol content of the blood was determined after operation only, it is reasonable to assume that the values were high or at least normal before operation. This assumption is supported by the fact that in case 19 the cholesterol content of the blood, which was 0.140 per cent on the day following the operation, had risen to 0.160 per cent 14 days later.

High or normal values for the cholesterol content of the blood are thus seen to be the rule in cases of prostatic enlargement, low values being exceptional.

In two of the cases (6 and 21) the condition was malignant, but there was nothing in the values obtained to distinguish them from the benign cases. The high values obtained in a third of the cases do not appear to be related in any way to the genito-urinary condition, or the urinary retention present. Doubtless the hypercholesterolaemia is associated with the existence of marked vascular degeneration, for all the patients were middle-aged or elderly men.

Cases 2 and 16 are examples in point. These patients, whose blood cholesterol values were 0.247 per cent and 0.354 per cent, died and post mortem examinations in both cases revealed the presence of well-marked atheromatous changes.

The low values, on the other hand, are very significant. The patients with hypocholesterolaemia all died, and in all of them post mortem examination revealed the presence of some form of septic infection of the urinary tract.

These observations would lead one to suggest that blood cholesterol determinations on cases of prostatic enlargement before operation may be of value to the surgeon. The presence of a hypocholesterolaemia should make one suspect a septic condition of the urinary tract and may thus serve as a warning and guide to the surgeon.

As seen from Tables VI(a) and (b), no parallelism was found to exist between the cholesterol and the urea nitrogen content of the blood. This is as would be expected, since retention of nitrogen

TABLE V1.(b).

Case.	Age.	Sex.	Clinical Diagnosis.	Cholesterol in per cent.	Urea in mgms/ 100 c.c.	REMARKS.
1. F.H.	39	♂	Urethral Stricture	0.190	25.2	Bougie passed; attends as out patient.
2. M.Tr.	49	♂	" "	0.160	25.2	" " " " " "
3. H.Th.	43	♂	Prostatis & Cystitis	0.150	33.6	Bladder washed out; " " " " "
4. T.M.	64	♂	Carcinoma of Bladder	0.210	22.4	Large fixed growth on superior surface of bladder - inoperable.
5.S.T.G.	40	♂	T.B. Testis, Prostate and Urethra.	0.177	16.8	
6. F.K.	44	♂	Vesical Calculus	0.200	19.6	Suprapubic lithotomy, drainage. Well.
7. C.B.	57	♀	Ureteral Calculus.	0.199	16.8	
8. M.S.	51	♀	Renal colic;movable kidney	0.222	22.4	
9. K.M.	42	♀	Congenital Cystic Kidney.	0.207	33.6	
10. J.D	36	♀	Pyelitis	0.120	22.4	
11. S.M.	17	♂	Pyelitis	0.130) Duplicate 0.132)	22.4	
12. J.H.	57	♂	Uraemia	0.266	Not done.	Improved.
				0.282 a month later.	" "	
13. M.M.	43	♀	Uraemia	0.242	" "	Died P.M. findings: Extreme interstitial Nephritis with associated cardio, wiscular changes.
14. W.W.	55	♂	Arterioselerosis	0.259		Systolic blood pressure 250 m.m.
15. F.N.	14	♂	Chronic Interstitial Nephritis	0.450		
16. Th.D.	54	♂	Hypernephroma	0.157		Nephrectomy. Well.

in the blood, depends on deficiency in renal function, and is not necessarily influenced by the presence or absence of a septic condition of the genito-urinary tract.

The cases in Group VI(b) include these genito-urinary conditions other than these associated with prostatic enlargement, and require but little comment. Normal values were obtained in the two cases of Urethral stricture. A high value (0.210 per cent) was obtained in Case 4 with carcinoma of the bladder and this is in accordance with Luden's results.

In the one case of hypernephroma (16) the cholesterol content of the blood was normal. The two Pyelitis cases (11 and 12) were conspicuous by their low values, and this is in accordance with the results obtained in Group VI(a).

In the 2 cases of Uraemia (12 and 13) examined, a marked hypercholesterolaemia was present, a result similar to that obtained by other workers. It is interesting to note that in Case 13 the cholesterol content of the blood just before death was as high as 0.242 per cent. Baumeister and Henes (1913)[36] found that in one case of Uraemia just prior to death the cholesterol content of the blood fell to 0.090 per cent.

TABLE VII (a) SECONDARY AND PERNICICUS ANAEMIA.

CASE.	AGE.	SEX.	DISEASE.	CHOLESTEROL IN PER CENT. PLASMA	CORPUSCLES	ERYTHROCYTES.	HAEMOGLOBIN in per cent.	COLOUR. INDEX	LEUCOCYTES.	REMARKS.
Average Normal value				0.162	0.110					
1. A.S.	53	♂	2ndary Anaemia after Haematemesis.	0.157		3,400,000	45	0.73	4,800	
2. J.H.	5	♂	2ndary Anaemia	0.120		3,900,000	40	0.5	6,000	
3. J.B.	45	♂	2ndary "	0.128	0.082	2,800,000	50	0.9	3,800	
4. Mrs. A.S.	33	♀	2ndary " following metrorrhagia	0.090		2,000,000	25	0.6	4,200	
5. Mrs E.T.	35	♀	2ndary Anaemia							
			4 months later. ↘	0.103	0.119	980,000	18	0.9	3,300	
			↘	0.122		4,800,000	75	0.75	6,600	
6. Mrs A.M.	49	♀	Anaemia of syphilitic origin	0.175		3,900,000	35	0.47	2,300	
7. A.W.	34	♀	Pernicious Anaemia, 3 ↘	0.107	0.070	1,800,000	35	1.0	2,600	
			months later. →	0.090		1,000,000	20	1.0	3,600	
8. A.M	30	♀	Pernicious Anaemia.	0.070		800,000	15	0.9	2,800	(Case 8) Died. P.M. findings: Erythroblastic reaction of bone marrow etc.
9. A.F.	38	♀	" "	0.140	0.080	2,400,000	50	1.0	5,600	
10. H.H.	48	♂	" "	0.132	0.117	2,700,000	55	1.1	6,400	
11. J.S.	54	♂	" "	0.072		900,000	20	1.1	3,000	
12. E.P.	33	♂	" "	0.131	0.081	2,200,000	40	1.0	6,500	
			3 weeks later	0.110	0.077	3,400,000	68	1.1	5,200	

CONDITIONS ASSOCIATED WITH SPLENOMEGALY.

Table Vii. (b)

CASE	AGE.	SEX.	DISEASE	CHOLESTEROL IN PER CENT PLASMA	CHOLESTEROL IN PER CENT CORPUSCLES	ERYTHROCYTES.	HAEMOGLOBIN.	COLOUR INDEX	LEUCOCYTES.	REMARKS.
1.Mrs W.	35	♀	Myeloid Leucaemia	0.104		3,200,000	40	0.63	210,000	
2.J.B.	57	♂	" "	0.127		5,100,000	70	0.77	220,000	
			6 weeks later	0.109		5,000,000	60	0.60	10,000	After X Ray treatment.
3.W.J.	67	♂	Lymphatic Leucaemia	0.108		2,800,000	20	0.4	900,000	Died 2 months later.
4.Th.W.	55	♂	Myeloid "	0.099		4,500,000	55	0.66	280,000	
5.W.A.	56	♂	" "	0.090		4,000,000	45	0.63	110,000	
6.Mrs.B	28	♀	Familial Acholuric Jaundice	0.094		2,600,000	40	0.08	3,800	
7.J.W.	60	♂	" " "	0.097	0.077					Father of Mrs.B.
8.S.G.	28	♀	" " "	0.112	0.105	3,000,000	40	0.60	6,400	
				0.104	0.110				7 days later.	
9.H.G.C.	20	♂	" " "	0.060		4,250,000	70	0.82		
10.S.P.	37	♂	Splenic Anaemia	0.121		3,700,000	45	0.67	1,700	
				0.123					10 days later.	
11.W.M.	14	♂	Portal Cirrhosis	0.087	0.107	6,200,000	85	0.7	10,200	
12.R.R.	55	♂	Polycythaemia Vera	0.074	0.121	9,500,000	115	0.67	21,200	
13.M.H.	30	♀	"	0.190	0.140	7,700,000	115	0.75	9,800	

Group VII.

12 cases of Anaemia were examined, including 6 cases of Pernicious Anaemia. The values obtained for the cholesterol content of the blood and the blood counts are recorded in Table VII(a).

Under "Cases associated with Splenomegaly" are included 5 cases of Leucaemia, 4 cases of Acholuric family jaundice, 1 case of Splenic Anaemia, 3 cases of Portal Cirrhosis and 2 cases of Polycythaemia Vera. The values obtained in these cases are given in Table VII (b), while a comparison of the values obtained in 4 of the cases before and after splenectomy is given in Table VII(c).

A detailed account of the case histories will be found in the Appendix.

For convenience the 2 cases of Polycythaemia will be discussed separately, but the remaining cases will be considered together.

If we take 0.162 per cent as the average normal value for cholesterol in the plasma, and 0.110% as the average normal content of the corpuscles it will be seen that the values for cholesterol in the plasma are strikingly low in primary and severe secondary anaemias. In the corpuscles, too, some low values have been obtained, but the variations are only slight. In 2 cases only viz. case 5. Table VII(a), and case 11 Table VII(b), the cholesterol content of the corpuscles is seen to be increased relatively. Unfortunately, the cholesterol content of the corpuscles was not determined in all the cases, owing to an insufficiency of blood.

Of the cases in Group VII(a) the lowest values were obtained in numbers 4, 5, 7, 8 and 11, in which the anaemia was most pronounced. The values obtained in Cases 1 and 6 support the

observation of Bloor (1917), that the blood cholesterol content is normal or only slightly subnormal as long as the percentage of red corpuscles in the blood does not fall below 50% of the normal figure.

It is interesting to note that a higher value for the cholesterol content of the blood was obtained in Case 5, where the anaemia was very marked, than in case 4 with a less pronounced anaemia. Case 5 ultimately made an excellent recovery, and the blood picture 3 months afterwards was practically normal.

There appears to be no characteristic difference in the cholesterol content of the blood in the different types of anaemia.

In individual cases there is seen to be a parallelism between changes in the number of corpuscles and the per centage of haemoglobin on the one hand, and the cholesterol content of the blood on the other. This is seen in cases 5 and 6 (Table VII a) and in three of the cases of Acholuric family jaundice and the one case of Splenic Anaemia examined. Case 12, Table VII(a) is an exception, for with improvement in the condition of the blood, there is a fall in the cholesterol content of the blood. It should be noted, however, that the patient's general condition at the time of the second blood examination was considered to be worse than at the previous examination, instead of being better, as the blood examination would have led one to suppose. This observation would seem to support the view expressed by McCrudden and Sargent (1916) that low cholesterol values are a general accompaniment of lowered vitality. Further support to this view is lent by the low value of (0.107%) obtained in case 11 (Table VII-b.) associated with

TABLE VII. (c) THE EFFECT OF SPLENECTOMY ON THE CHOLESTROL CONTENT OF THE BLOOD.

CASE	AGE	SEX	DISEASE	Time in relation to SPLENECTOMY	CHOLESTEROL IN PER CENT PLASMA	CHOLESTEROL IN PER CENT ERYTHROCYTES CORPUSCLES	ERYTHROCYTES.	HAEMOGLOBIN IN PER CENT	COLOUR INDEX	FRAGILITY TEST INITIAL. (1 per cent Saline)	FRAGILITY TEST COMPLETE.	REMARKS
1. Mrs.B.	28	♀	Acholuric family Jaundice.	6 weeks before	0.094	-	2,600,000	40	0.8			Urobilin in urine
				2 " "	0.126	0.102	3,000,000	45	0.75	0.600	0.425	After blood transfusion.
				on day of operatn.	0.200	0.086	4,500,000	60	0.7	0.500	0.450	After second transfusion.
				10 days after.	Blood from splenic vein					0.725	0.525	
					0.162	0.080				0.625	0.450	Urobilin
				14 " "	0.199	0.102				0.650	0.525	" absent.
				21 " "	0.222	0.107				0.625	0.450	
2. S.G.	28	♀	" " "	9 days before	0.112	0.105	3,000,000	40	0.67	0.550	0.500	Urobilin in +
				At operation	0.105			From splenic vein.		0.725	0.625	(urine.
				1 week after	0.109	0.090				0.550	0.500	Urobilin absent.
				3 weeks after	0.171	0.108						
				6 " "	0.197	0.108	5,000,000	68	0.68			
				11 " "	0.234	0.119	5,800,000	80	0.7			
3. A.J.C.	20	♂	" " "	At Operation.	0.060		4,250,000	70	0.82			
				8 days after	0.067		5,000,000	85	0.85			
				15 " "	0.087							
				21	0.094							
4. S.P.	37	♂	Splenic Anaemia	19 " before	0.123		3,700,000	45	0.67			
				9 " after	0.113	0.095						
				19 " "	0.142	0.108	4,200,000	45	0.6			
				39 " "	0.181							
				59 " "	0.160							
				86 " "	0.200							

a blood count of 6,200,000 and a haemoglobin per centage of 85, and where there was no fever to account for the very low value. In the 5 cases of leucaemia, too, the cholesterol values were not proportionate to the degree of the anaemia, as examination of the first 5 cases of Table VII(b) will show. In leucaemia the cholesterol values also fail to show any parallelism to the leucocyte count. Thus, in case 2 Table VII(b) with a leucocyte count of 220,000 the value for the cholesterol content of the blood was 0.127 per cent; 6 weeks later, in the same case, when, under the influence of X-ray treatment the leucocytes had become reduced to 10,000 and the size of the spleen had become much reduced, the cholesterol content of the blood fell to 0.109 per cent. It is significant that the anaemia had become more pronounced.

In the 4 cases of Acholuric Family jaundice and the one case of Splenic Anaemia examined, low values were obtained for cholesterol in the plasma, while the corpuscular content was normal or slightly below normal.

Following splenectomy, if we exclude the fall observed in cases 1 and 4, Table VII(c) shortly after the operation, a result which is to be attributed to the immediate post-operative effects, there occurred a steady rise in the cholesterol content of the plasma, and a very slight increase in that of the corpuscles. King (1914) (79), in experiments on dogs, found that after splenectomy there occurred an increase in the cholesterol content of the plasma at the expense of the corpuscles. King only determined the cholesterol content of the corpuscles in one case, while in the cases under discussion the cholesterol content

of the corpuscles was determined in three cases, and in two of these 5 successive analyses were made on the corpuscles (cf. Table VII c).

Bloor (1917)(44) in 4 cases of Pernicious Anaemia, and 2 cases other than anaemia found that after splenectomy there were increases in the cholesterol content of the plasma in all but one case, but that the corpuscular content remained unaltered. Bloor's method of determining the cholesterol content of the corpuscles, however, appears to be liable to greater error than my own. He does not make a direct determination, but computes the value from the difference between the figures obtained for the cholesterol content of the whole blood and the plasma, and the percentage of corpuscles as calculated after centrifugalisation in graduated tubes.

Simultaneously with the increase in the cholesterol content of the blood following splenectomy, there is also a great improvement in the general condition of the patients, and a marked improvement in the blood count. This was particularly striking in the 3 cases of Acholuric Family Jaundice. The patients who had been jaundiced all their lives, lost their icterus almost immediately after the operation; urobilin which had been present in the urine, disappeared, while the blood plasma which contained appreciable quantities of bilirubin before operation, was perfectly free from bile pigments after splenectomy. Case 1 (Table VIIc) had had several attacks of what appeared to be biliary colic; at operation gallstones were found in the gall-bladder, but her condition did not admit of their removal. Yet, after operation these attacks ceased; this supports the observation made by Giffin (1917)(77)

in a review of 17 cases of Haemolytic Jaundice from the Mayo Clinic, that patients after splenectomy may improve remarkably although retaining their gall-stones, but that, on the other hand, removal of the gallstones in a case of haemolytic jaundice does not cure the condition.

The improvement following splenectomy in cases of Acholuric Jaundice was reported by Banti as early as 1903, when a complete and permanent cure was effected by splenectomy in one of his own cases, and in the cases of Micheli and Umber. In splenic anaemia, too, the improvement after splenectomy has been noted by Giffin (1913)(78) in a review of 18 cases from the Mayo Clinic.

Eppinger also found ina series of clinical conditions associated with haemolysis that removal of the spleen produced a beneficial effect on jaundice and anaemia, that is symptoms which are associated with haemolysis. King(1914)(79) who is of the opinion that in cases associated with haemolysis there is an excessive activity of the haemolytic function of the spleen, which he terms "hypersplenism", describes the influence of the spleen on haemolysis, anaemia, and icterus thus -

Hypersplenism.	Asplenism.
High content of unsaturated fatty acids in blood.	Low content.
Haemolysis	Greater resistance to haemolytic agents.
Anaemia	Improvement of the anaemia.
Icterus.	Difficulty in producing jaundice by haemolytic agents.

King has determined the unsaturated fatty acid content of the blood (Iodine value) in 3 cases of Pernicious Anaemia, and in 2 cases of Acholuric Jaundice, while he has also followed the effects of splenectomy on this value. He was stimulated to do this work by the suggestive results obtained by Faust and Tallquist[80] in the anaemia produced by the tapeworm - Dibothriocephlus latus. These workers demonstrated the presence of a haemolytic substance in the worm which they isolated and found to be cholesterol oleate. They further showed that the haemolytic properties were due entirely to Oleic Acid and that a strongly haemolytic chyle, owing its haemolytic properties to abnormal amounts of sodium oleate, could be obtained in dogs by feeding oleic acid. Faust (1908)[81] also produced anaemia experimentally in dogs and rabbits by long continued feeding with oleic acid. Oleic acid being an unsaturated fatty acid, the haemolysis produced by it was ascribed to the presence of the double bond. McPhedran (1913)[82] found that no parallelism existed between the haemolytic activity and the degree of unsaturation of the unsaturated acids, and he concluded that there was no evidence of the presence in the human body at any time of fatty acids appreciably more haemolytic than oleic acid. King in the 5 cases associated with haemolysis examined by him found a great increase in the unsaturated fatty acid content of the blood (High Iodine Value) and also a low cholesterol content of the blood. He concludes that "there appears to be a parallelism between highly unsaturated fatty acids in the blood and haemolysis, and that further the haemolysis is more marked because of the small amount of antihaemolytic

substance - (cholesterol) present in the blood of those cases.

The interpretation of the low cholesterol values is thus far from clear. McCrudden and Sargent (88) believe that they are the result of a lowered vitality, Since they found that low cholesterol values were the usual accompaniment of a lowered vitality, whereas King and Eppinger connect the low values with haemolysis.

As pointed out by Bloor, though cholesterol acts as an antihaemolytic agent against such substances as saponin, tetanolysin and cobra-venom there is no evidence to show that it protects against haemolysis by the unsaturated fatty acids. The fact that improvement in the clinical condition generally resulted in increased cholesterol values might be taken as supporting either explanation.

One important point emerges from these observations, namely the relation of the spleen to the low cholesterol values. The removal of the spleen was followed, in the 4 cases of haemolytic jaundice and splenic anaemia described by me by an increase in the cholesterol of the blood of 1. A similar finding has been recorded by Bloor (114), in 4 cases of Pernicious Anaemia treated by splenectomy, and also by King (79) in his experimental work on dogs.

The association of a low cholesterol value with a high iodine value of the blood and conversely of a high cholesterol value and a low iodine value (King) is very suggestive.

If we assume that Lifschütz (23) is correct in his claim that cholesterol may be formed from Oleic Acid, then one may put forward the hypothesis that the spleen, in cases associated with haemolysis, exerts a perverting influence on cholesterol metabolism,

preventing the conversion of oleic acid to cholesterol, since, after removal of the spleen, there is a fall in the iodine number and a rise in the cholesterol content of the blood.

Interesting results were obtained in the two cases of polycythaemia rubra examined. If low cholesterol values are a characteristic feature of severe anaemia one would expect high values in polycythaemia. This was not found to be the case. Thus, in one case (Case 12 - Table VIIb) with a red cell count of 9,500,000 and a haemoglobin percentage of 115, the cholesterol content of the plasma was 0.074 per cent (half the normal value). This was confirmed on two subsequent examinations. The corpuscular content was about normal (0.121 per cent) In the second case (Case 13, Table VIIb) with a red cell count of 8,000,000 and a haemoglobin per centage of 110, the cholesterol content of the plasma was 0.190 per cent and of the corpuscles 0.140 per cent, that is slightly above the normal value.

These findings are contrary to those of Pribram (1921)(83) who found an excess of cholesterol in the blood in a case of splenomegalic polycythaemia rubra and in a case of secondary polycythaemia connected with pulmonary emphysema. Pribram and Walter (1912)(84) also described two cases of acute yellow atrophy of the liver (one genuine form, the other due to septic infection) in both of which examinations of the blood showed a polycythaemia rubra, and a high cholesterol content of the blood serum. Taking these observations in conjunction with those of Reicher,(145) who was able to increase the erythrocyte count in 4 cases of anaemia to 6,000,000 per cubic millimetre, by feeding with cholesterol, and the results of P. Thomas and M.Lebert (1912)(85)

who succeeded in experimentally increasing the erythrocytes in the blood of guinea-pigs and rabbits by injections of an emulsion of cholesterol oleate, Pribram concludes that excess of cholesterol in the blood delays the normal destruction of erythrocytes.

The theory that increased durability of the erythrocytes is an aetiological factor in the production of polycythaemia is opposed by the observations of Parkes-Weber and Saundby, and of Vaquez and Laubry on the resistance of the red blood cells to haemolysis.

Parkes-Weber and Saundby, in 2 cases of polycythaemia rubra, found that the resistance of the red blood cells to haemolysis, as examined by the method of Ribierre, was about normal, while Vaquez and Laubry in one case examined, found it to be unduly low. Abeles in two cases examined found the excretion of iron in the urine to be above normal, an observation which supports the view that increased haemolysis accompanies absolute polycythaemia.

In one of the cases described by me the fragility of the red cells was tested by Dr. W. MacAdam and was found to be increased (vide appendix).

The cholesterol findings in these two cases, as well as the increased fragility of the red cells, would seem to support the view of Parkes-Weber and others, that excessive formation of red blood corpuscles in the bone marrow, and not increased durability of the red cells, is the primary pathological condition in polycythaemia vera. And, indeed, that this condition is brought about by increased activity of the bone marrow is evidenced by the results of post mortem examinations on cases of

polycythaemia vera. These have shown the marrow of the long bones to be red and still actively engaged in the formation of erythrocytes, instead of being yellow and fatty as most of it is in healthy adults.

Moreover, evidence in favour of the view that Polycythaemia Vera is due to increased haemopoietic activity of the bone marrow, is furnished during life by the high per centage of polymorphonuclear leucocytes, and the occasional presence of erythroblasts and myelocytes in the circulating blood, and in 2 cases (G.A.Gibson 1908, Watson Wemyss 1911 & 1913) quoted by Parkes Weber by direct examination of the marrow of a long bone (biopsy method)

In the 2 cases described by me no myelocytes or nucleated reds were detected, but in one case (Case 12, Table VIIb) there was a marked increase in the polymorphonuclear leucocytes (84.6%).

Further support in favour of the view that polycythaemia vera is due to increased activity of the haemopoietic tissues is lent by the fact, that in one of the cases described by me (Case 12. Table VIIb) after the venesection (400 c.c. withdrawn) the blood count was practically unchanged the following day.

General Summary with Conclusions.

This investigation of the cholesterol content of the blood in many and varied pathological conditions has given results which, on the whole, are in accordance with these of other workers. Certain new points of considerable interest have presented themselves, while some of the findings afford evidence in connection with several of the moot points with regard to the physiology and pathology of cholesterol metabolism.

Before briefly discussing these more general questions, I give a summary of my main findings in the various groups of conditions examined.

I In 12 normal cases examined the cholesterol content of the blood plasma was found to vary from 0.133 - 0.191 per cent, giving an average of 0.162 per cent.

II In pregnancy a hypercholesterolaemia was observed in the 4 cases examined, the values obtained ranged from 0.196 - 0.288 per cent. The increase appeared as early as the second month of pregnancy. In one case, 4 months after delivery, the cholesterol content of the blood was found to be normal (0.170 per cent)

III In typhoid fever, 4 cases, low values (0.100 - 0.120 per cent) were obtained for the cholesterol content of the blood plasma in the febrile stage of the disease. In the early convalescent stage a hypercholesterolaemia was noted in 2 cases examined, and in one case in which a third determination was made, the cholesterol content of the blood was found to have returned to normal (0.160 per cent) towards the end of convalescenence.

Typhoid fever was thus seen to behave like the other fevers and did not prove to be the exception that previous workers have stated it to be.

The discrepancy between my own findings in this connection and those of other workers may possibly be explained by the fact that, e.g. Chauffard, Laroche (Richet) and Grigaut (67) and others had determined the cholesterol content of the blood only in the convalescent stage, when a hypercholesterolaemia is present.

IV In Cholelithiasis a hypercholesterolaemia (0.193 - 0.289 per cent) was observed in 7 cases; while in 5, normal values were obtained. One case, which was diagnosed clinically as Cholelithiasis and in which a very low value was obtained for the cholesterol content of the blood, proved to be a case of appendicitis. In 4 cases, blood cholesterol determinations were made within a fortnight after operation, a fall in the cholesterol content of the blood was constantly found, a finding which I have consistently obtained in various conditions after surgical procedures.

One case was hypercholesterolaemic $4\frac{1}{2}$ months after operation.

V In conditions associated with Glycosuria 4 cases of Diabetes Mellitus and 1 case of "Renal Glycosuria" were examined. A parallelism was observed between the cholesterol and sugar content of the blood.

A normal sugar content in 2 cases was associated with a normal cholesterol content of the blood. On the other hand, in 2 cases with hyperglycaemia there was an associated hypercholesterolaemia. In one case several successive determinations were made and the improvement in

the patient's condition under dietetic treatment was seen to be accompanied by a reduction in the hyperglycaemia and a fall in the cholesterol content of the blood.

VI Interesting results were obtained in the cases(23) of prostatic enlargement examined.

High (0.354 - 0.133 per cent) or normal values were obtained in cases uncomplicated by sepsis.
In the presence of a septic infection of the urinary tract, 5 cases, low values (0.126 to 0.070 per cent) were obtained

No relationship was found to exist between the cholesterol and urea nitrogen content of the blood.

So far as I am aware no previous work has been done on the relation of the cholesterol content of the blood to sepsis in genito-urinary conditions.

In the genito-urinary conditions, other than prostatic enlargement, the results obtained were similar to those of other workers. High values (0.242 - 0.450 per cent) were noted in uraemia, arteriosclerosis and Chronic Bright's Disease.

In one case of uraemia just before death the cholesterol content of the blood was still as high as 0.242 per cent.

VII(a) In primary and secondary anaemia (12 cases) low values were obtained in the cases with pronounced anaemia. Where the anaemia was not marked the cholesterol content of the blood was approximately normal. Only slight variations were observed in the cholesterol content of the corpuscles in the various types of anaemia.

VII (b) The conditions associated with splenomegaly comprise 5 cases of Leucaemia, 4 of Acholuric Family Jaundice, one

case of Splenic Anaemia, 2 cases of Polycythaemia and one of Portal Cirrhosis (in child).

Low values (0.127 - 0.090 per cent) were obtained in all the cases of Leucaemia. The degree of anaemia present was scarcely sufficient to account for these low values.

In the 4 cases of Acholuric Jaundice examined the cholesterol content of the blood was low (0.60 - 0.112 per cent).

Blood transfusion in one case raised the cholesterol content of the blood plasma from 0.094 to 0.126 per cent, after the first transfusion, and to 0.200 per cent after the second transfusion.

Splenectomy was followed by a steady and marked increase in the cholesterol content of the plasma and to a very slight extent in the corpuscles. This was observed in all the splenectomised cases - 3 cases of Acholuric Jaundice, and 1 case of Splenic Anaemia. The rise was very considerable so that from being hypocholesterolaemic these patients became hypercholesterolaemic.

In Polycythaemia a low value (0.074 per cent) for the cholesterol content of the plasma was obtained in one case, and in the other the value was normal. These findings are contrary to those of previous workers, but they are in accordance with the recent views as to the pathogenesis of the disease, namely, that it is due to excessive activity of the haemopoietic tissues, and not to increased durability of the red cells.

The salient feature of this investigation from the diagnostic and prognostic aspects are.

(1) In cases clinically diagnosed as cholelithiasis the finding of a low value for the cholesterol content of the blood should make one suspect some other condition.

(2) Successive blood cholesterol determinations, before and after operation, may be of undoubted value in the prognosis and subsequent treatment of cases of Cholelithiasis.

These cases may be subdivided into 2 groups.

I. Cases with a normal cholesterol content of the blood.

II. Cases which are hypercholesterolaemic.

(a) obstructive hypercholesterolaemia - temporary - stone - stricture, new growth.

(b) Diathetic hypercholesterolaemia:

with obstruction
without obstruction } Intermittent and permanent.

In cases with a normal cholesterol content of the blood, the gallstones are a relic of a former hypercholesterolaemia. These patients will probably never have a recurrence unless the same physiological and pathological condition, which originally caused the hypercholesterolaemia, should return.

The obstructive hypercholesterolaemias are temporary, the cholesterol content of the blood returning to normal with the removal of the obstruction.

The diathetic group of cases, on the other hand, are more or less continuously hypercholesterolaemic.

It appears to be a distinct advantage to determine the cholesterol content of the blood of every case of cholelithiasis

before and after operation.

In the presence of a hypercholesterolaemia provision should be made for drainage of the biliary passages, in order to deplete the body of the retained lipoids. After removal of the drainage tube the blood should again be examined, and if the cholesterol content of the blood is high, the patient belongs to the diathetic group. Further accumulation of cholesterol can be controlled by dietetic measures, since the cholesterol content of the blood depends on that of the food ingested.

(3) It is well known that in cases of prostatic enlargement it is often impossible, from the clinical examination alone, to determine the presence or absence of a low form of infection of the upper urinary tract. Here blood cholesterol determinations may be of considerable value in helping the surgeon to decide as to the advisability of undertaking the major operation of prostatectomy.

A low value in cases of prostatic enlargement may indicate the presence of septic infection of the upper urinary tract, and such a finding may serve as a warning and guide to the surgeon.

(4) In profound anaemias the finding of a value for the cholesterol content of the blood which is higher than would be anticipated from the blood count, is of favourable prognostic significance, the patient tending to recover under appropriate treatment.

Suggestions in connection with the physiology and pathology of cholesterol metabolism.

(1) The low value for the cholesterol content of the blood in the acute stage of typhoid fever as in all other fevers, and the manifestation of a hypercholesterolaemia in the early convalescent stage support the view that cholesterol plays an important part in immunity and is intimately connected with the protective mechanism of the body.

Further the low values found after surgical procedures would also favour the above view.

(2) The increase in the cholesterol content of the blood after splenectomy in cases associated with haemolysis.seems to indicate that the spleen is in some way concerned with cholesterol metabolism.

(3) The association of a low cholesterol content with a high unsaturated fatty acid content of the blood, (79) and vice versa seems to point to some intimate chemical relationship between the unsaturated fatty acids and cholesterol.

This observation, taken in conjunction with that of Lifschutz that in vitro, oleic acid, which is an unsaturated fatty acid, on oxidation becomes in part converted into cholesterol, suggests the possibility that in the body, cholesterol may be formed from oleic acid.

If we accept the above hypotheses then the following deduction appears quite plausible, namely, that in conditions associated with haemolysis the spleen exerts a perverting influence on cholesterol metabolism, preventing the change of oleic acid into cholesterol. This allows the unsaturated fatty acids to accumulate in the blood, which may be the cause of the haemolysis.

In conclusion I wish to acknowledge my indebtedness to Professor M. J. Stewart, for granting me the privilege of working in his department; to Dr. W. R. MacAdam under whose supervision this work was carried out. I also have to acknowledge my thanks to Dr. W. MacAdam for permission to quote the results of the blood counts, fragility tests, and blood urea nitrogen estimations.

My thanks are also due to the physicians and surgeons of the Leeds General Infirmary for allowing me to make use of their cases.

APPENDIX.

Resumés of Case Histories.

Typhoid Fever.

Case I. L.B. female, aged 17, was admitted to the wards of the Leeds General Infirmary, under the care of Dr. Veale, on 28th October, 1921, with a history of headache, listlessness and marked constipation of 14 days' duration.

On admission she was seen to be a thin, pale girl. Rose coloured spots were present on the abdomen and the front and back of chest. The abdomen was tumid, but there was no tenderness and the spleen could not be felt. There was a leucopenia, the leucocyte count being 4,300 per c.mm. Bacillus Typhosus was recovered from the urine and faeces. The cholesterol content of the blood on 1st November, 1921, that is on the 17th day of illness, was 0.100 per cent. On that day the temperature was 104°F., the pulse and respiration rates being 120 and 30 respectively. 23 days later, after the patient had been free from fever for 2 days, the cholesterol content of the blood was again determined and was found to be 0.190 per cent. A third blood cholesterol determination was made 18 days afterwards and was found to be 0.160 per cent.

Case II.

F.H., male, aged 14, was admitted to the Leeds General Infirmary, under the care of Dr. Watson, on 16th October, 1921, complaining of abdominal tenderness and a sensation of fulness in the lower abdomen, of 9 days' duration.

On admission he was seen to be a well developed boy, with flushed face and sordes about the mouth. The abdomen was tumid and covered with rose spots. The spleen could just be felt. There was a marked leucopenia, the leucocyte count being 2,700. The Widal Reaction was positive. On 30th November, 1921, that is on the 14th day of illness the blood cholesterol content was 0.120 per cent. The temperature on that day was 102.8°F., the pulse and respiration rate being 106 and 30 respectively. A second blood cholesterol determination was made on 17th December, 1921, 3 days after the subsidence of the fever and was found to be 0.200 per cent.

Case III.

This was a patient in the 3rd week of illness, and was in the Typhoid wards of the Corporation Fever Hospital, Leeds. No further history was obtained.

The blood cholesterol content in the 3rd week of illness was 0.120 per cent.

Case IV.

Nurse D. contracted the disease while attending on an enteric fever patient. After an illness of 60 days she died. At the post mortem examination, in addition to the usual morbid changes, there was found a perforation of the ileum with localised abscess formation, and a toxic myocarditis.

Blood was obtained from the Inferior Vena Cava after death, and the blood cholesterol content was found to be 0.100 per cent.

CHOLELITHIASIS.

Case I.

H.M., male, aged 61, a painter, was admitted to the Leeds General Infirmary, under the care of Sir Berkeley Moynihan, on 25th October, 1921, with a history of pain in the middle of the abdomen of 2½ months' duration. There had been slight jaundice.

On admission, except for slight icterus there was nothing abnormal to be made out on physical examination.

The cholesterol content of the blood on 29th October, was 0.193 per cent.

He was operated on 4th November when the gall-bladder was found to be enlarged and full of stones, one being impacted in the cystic duct. The gall-bladder was removed and a drainage tube was inserted in the cystic duct. On 13th November, that is a week after the operation, the cholesterol content of the blood was again determined and was found to be 0.127 per cent. The patient left Hospital the following week. Unfortunately he lived too far away to be recalled for further blood examinations.

Case II.

J.J.F. male, aged 41, a carter, was admitted to the Leeds General Infirmary under the care of Sir Berkeley Moynihan, on 8th November, 1921, complaining of attacks of severe pain in the right hypochondrium of 2 months' duration. He had been slightly jaundiced during and after an attack. The physical examination, on admission, was entirely negative. The cholesterol content of the blood on 11th November was 0.230 per cent.

At operation on 15th November a number of small facetted gallstones

were found and removed. He was discharged a fortnight later. He was seen again in the Out-patient Department on 23rd March 1922, that is 4½ months after operation, when he was in excellent health. The cholesterol content of the blood plasma was 0.215 per cent, and the red blood corpuscles 0.098 per cent.

Case III.

Mrs. W.E. aged 38, was admitted to the Leeds General Infirmary under the care of Mr. Collinson on October 1921, with symptoms of cholelithiasis. The cholesterol content of the blood on 1st November, 1921, was 0.147 per cent.

At operation on 9th November, the diagnosis of cholelithiasis was confirmed.

Case IV.

Mrs. E.N. aged 43, was admitted to the Leeds General Infirmary under the care of Mr. Collinson, on November 1921. A diagnosis of cholelithiasis was made and this was confirmed at operation on 7th November, 1921. The cholesterol content of the blood on 5th November, that is 2 days before operation was 0.168 per cent.

Case V.

Mrs. K.C., aged 37, was admitted to the wards of the Leeds General Infirmary complaining of abdominal pain in the right hypochondriac region. There was a history of jaundice. A diagnosis of cholelithiasis was made which was confirmed at operation. The cholesterol content of the blood on 28th November, 1921, prior to the operation, was 0.198 per cent.

Case VI.

Mrs. M.J.C. aged 56, was admitted to the Leeds General Infirmary under the care of Mr. Dobson, on 19th November, 1921, complaining of recurrent attacks of severe pain in the right hypochondriac region, accompanied by vomiting of four weeks' duration. There had been no jaundice, The physical examination was entirely negative. On 20th November, 1921, the cholesterol content of the blood was 0.289 per cent. She was operated on the following day, when a cholecystotomy was performed; the gall bladder was found inflamed and full of debris.

On 30th November, that is 9 days after the operation, the cholesterol content of the blood was 0.100 per cent. On repeating 8 days later it was found to be 0.106 per cent.

Case VII.

Mrs. B.W. aged 54, was admitted to the Leeds General Infirmary, under the care of Mr. Collinson, on 4th January, 1922, complaining of pain in the right hypochondriac and right iliac regions and jaundice of 3 weeks' duration. Patient was under the care of Mr. Knaggs at the Leeds General Infirmary four years ago with the same complaint. She was operated on at that time, the gallbladder and appendix being removed. Since then she has had several attacks of pain in the right side of the abdomen and between the shoulder blades.

On admission, except for slight jaundice, there was nothing abnormal to be made out on physical examination.
On 6th January, 1922, the cholesterol content of the blood was 0.263 per cent. Patient was treated with aperients and felt much relieved on 11th January, 1922, when she was discharged.

Case VIII.

Miss P., aged 20, female, was admitted to the wards of the Leeds General Infirmary with symptoms of cholelithiasis.
On 1st February, 1922, the cholesterol content of the blood was 0.228 per cent. At operation, the same day, gallstones were found in the gall-bladder; these were removed and drainage was provided for.
The cholesterol content of the blood on 8th February, 1922, that is one week after operation, was 0.140 per cent.

Case IX.

B. L. female, aged 48, was admitted to the wards of the Leeds General Infirmary with symptoms pointing to biliary colic.

On 1st February, 1922, the cholesterol content of the blood was 0.188 per cent. At operation on 2nd February, 1922, the diagnosis of cholelithiasis was confirmed. The cholesterol content of the blood one week after operation was 0.131 per cent.

Case X

Mrs. M.D., aged 59, was admitted to the Leeds General Infirmary under the care of Mr. Richardson on 14th March, 1922, complaining of attacks of pain in the right hypochondriac region, occurring at intervals during the last 8 years. Jaundice has been present at times and on these occasions the stools have been clay coloured.

The physical examination, on admission, was entirely negative.

On 16th March the cholesterol content of the blood was 0.250 per cent.

She was operated on the following day; the gallbladder was exposed, its wall was thickened and it contained several stones; there was a perforation about the middle. The gallbladder was removed and a drainage tube was inserted into the cystic duct.

She was discharged on 1st April, much improved.

Case XI.

Mrs. N.W., aged 47, was admitted to the Leeds General Infirmary, with a diagnosis of gall-stones. This was confirmed at operation. The cholesterol content of the blood on the day preceding the operation was 0.163 per cent.

Case XII.

Mrs. M.E. aged 63, was admitted to the Leeds General Infirmary, under the care of Mr. Dobson, on 4th February, 1922, complaining of severe pain in the right hypochondriac region accompanied with bilious vomiting and followed by jaundice. Patient had had three such attacks during the last 3 years.

On admission patient was seen to be a very well developed and well nourished woman. Except for some tenderness in the region of the gall-bladder there was nothing of note to be made out. There was slight fever, the temperature ranging from 99 - 99.5°F., the pulse and respiration rates from 108 - 120 and 24 - 27.

The cholesterol content of the blood on 6th February 1922, was 0.156 per cent.

At operation 3 days later, the gallbladder was seen to be small and contracted; there were no calculi in the gallbladder or cystic duct. A cholecystectomy was performed and drainage was provided for.

The patient died 2 days later.

The post mortem examination revealed the presence of a bilateral Broncho-Pneumonia. A small bilirubin gall-stone was found near the ampulla.

Case XIII.

Mrs. A.M.F., aged 65, was admitted to the Leeds General Infirmary, under the care of Sir Berkeley Moynihan, on 29th December, 1921, with a history of pain in the umbilical and right hypochondriac and lumbar regions, following an operation for gall-stones 18 months ago.

There was nothing to be made out on physical examination.

The cholesterol content of the blood on 6th January, 1922, was 0.170 per cent.

On 6th January, 1922, the abdomen was opened through the old scar; a large solid mass was discovered, adherent to the anterior abdominal wall. An anterior gastro-enterostomy was performed. The patient died 2 weeks later.

At the post mortem examination there were found a circular neoplasm of the jejunum,=a=suppurative pylephlebitis and general peritonitis. There were metastatic deposits in the lungs.

Case XIV.

S.G., male, aged 43, a hawker, was admitted to the Leeds General Infirmary, under the care of Mr. Collinson complaining of paroxysmal attacks of pain in the right side, of 3 years' duration. There was no history of jaundice. The case was diagnosed as cholelithiasis.

On 4th December, 1921, the cholesterol content of the blood was 0.085 per cent. The temperature, pulse and respiration rates were normal at the time.

Case XIV (contd.)

On 7th December, an incision was made through the right rectus muscle. The gall-bladder and biliary passages were normal, there were no calculi. The appendix was thickened, injected, and nodular.

The patient died 6 days after the operation.

The post mortem findings were (1) localised peritonitis and (2) Acute pleurisy.

Case I. J.J., Male, aged 33, a gardener, was admitted to the Hospital, on 28th October, 1921, complaining of general weakness and loss of flesh of 2 years' duration. He had lost a stone in weight since the onset of the illness. Excessive thirst or hunger had not been a marked feature.

The physical examination, on admission was entirely negative.

The urine was acid, had a specific gravity of 1040, was loaded with urates and contained 4.5% of sugar. Acetone and Diacetic acid were present. There was no albumen.

On 2nd. November 1921 the blood cholesterol content was 0.260 per cent. The blood sugar content was not determined.

The patient left hospital, at his own request on the following day.

Case II.

W.E. Male, aged 37, was admitted to the Hospital on November 19th, 1921, complaining of excessive thirst of 2 months' duration. Patient gave an interesting history. He was quite well, when towards the end of 1920 he was medically examined for life insurance and told that he had sugar in the urine. On the advice of his doctor he was admitted to the Leeds General Infirmary where he remained for 10 days. Sugar was intermittently present in the urine. He remained

well until September 1921 when he began to suffer from polyuria and thirst. He had lost flesh and was easily fatigued.

On admission there was nothing of note to be made out on physical examination.

The urine was amber coloured, acid in reaction, had a Specific Gravity of 1037, contained 7.75 grains of sugar per ounce. Acetone was present. On 22nd. November the blood cholesterol content was 0.177 per cent, the blood sugar content being 0.11 per cent.

Case iii.

H.C. Female aged 47, was admitted to the Hospital, on 23rd. January, 1922, with a history of lassitude, excessive thirst, pruritiss and tingling sensations in the limbs of 12 months' duration.

Patient had been troubled with winter cough since childhood. 11 years ago she suffered from great thirst and pruritiss. She was in bed for 6 weeks at that time, since when she felt quite well until one year ago when the pruritiss returned.

On admission she was seen to be a thin, pale woman. The temperature was 99 degrees F., the pulse and respiration rates being 84 and 22, respectively. She had a frequent cough with a purulent expectoration. There was impairment

of the percussion note over the left apex with high pitched sibilant rhonchi. In left axilla there were low pitched sonorous rhonchi. The sputum contained numerous tubercle bacilli.

For the rest there was nothing of note.

The cholesterol content of the blood on 24th January, 1922 was 0.204 per cent, the blood sugar content being 0.26 per cent.

The patient was discharged on 10th February, feeling relieved.

CASE iv.

R.W. Male, aged 26, a chemist was admitted to the Hospital on account of thirst and polyuria.

On 20th October, 1921, the cholesterol content of the blood was 0.380 per cent, the blood sugar content being 0.35 per cent. The urine was loaded with sugar. Acetone and Diacetic acid were present. On 9th November the blood cholesterol content was 0.238 per cent, the blood sugar content was 0.17. per cent.

On 23rd. November the cholesterol content of the blood was 0.188 per cent, the blood sugar content 0.15 per cent.

Patient was at this time feeling well; he was on diet of 2,500 calories and the urine was free from acetone and sugar.

CASE V.

CASE V.

A.G. Female, aged 38, a domestic servant, was admitted to the Hospital under the care of Dr. Watson, on 6th., December, 1921. She was sent in for observation by her own doctor as a case of Diabetes. She was quite well until December 1920 when she began to tire easily. She was given a tonic by her doctor and she felt much better until February 1921 when she began to lose flesh and developed pains in the shoulder and across the chest, while the skin became unusually dry. She again consulted her own doctor who diagnosed Diabetes Mellitus and recommended her for admission to the Leeds General Infirmary.

The physical examination was entirely negative. The urine was pale, acid in reaction, the Sp.Gr. varied from 1028 to 1041, the quantity from 54 to 24 oz. in the 24 hours, the sugar from 6.6 to 17.6 grains per ounce. On 15th. December, 1921 the cholesterol content of the blood was 0.190 per cent. The blood sugar content on 7th and 9th. December was 0.098 and 0.072 per cent.

Patient was discharged on 23rd December 1921. She was seen in the outpatient department on 24th., April, 1922, when the sugar content of the blood was 0.07 per cent and the percentage of sugar in the urine was 5.8 per cent.

GENITO URINARY CONDITIONS.

(a) Prostatic enlargements, benign and malignant.

CASE 1.

B.W. Male, aged 62 was admitted to the Hospital on February 4th, 1922. complaining of difficulty in passing urine. He has had this trouble for the last 6 months, but the condition has steadily become worse.

On admission, except for a swelling on the anterior rectal wall which could be felt by digital rectal examination the physical examination was entirely negative. The urine was clear. There was no fever.

On 6th February, 1922, the cholesterol content of the blood was 0.215 per cent, the urea content of the blood was 25.2 mgms per 100 c.c. On 7th February a suprapubic prostatectomy was performed and the bladder was drained. The prostate was found to be the seat of benign glandular hyperplasia. Patient left hospital a month after admission feeling well.

CASE II.

J. H. Male, aged 62, was admitted to hospital on 30th January, 1922, complaining of excessive frequency of micturitism of 6 years' duration, but worse during the last few weeks.

On admission, except for a marked prostatic enlargement there was nothing abnormal to be made out on physical

examination. There was no fever and the urine was clear.

On the 1st February, 1922 the cholesterol content of the blood was 0.247 per cent. and the urea content of the blood was 16.8 ~~per cent~~. mgms per 100 c.c. Suprapubic prostatectomy was performed and provision was made for drainage. The patient died 12 days later.

The Post mortem findings were:

Oedema of lungs; coronary atheroma, a small gall stone in the cystic duct; old tubercular mesenteric glands.

CASE iii.

J.H.P. Male, aged 70, was admitted to the Hospital on 1st November 1921, complaining of inability to pass urine following an attack of diarrhoea 2 weeks prior to admission. He was catheterised daily by his own doctor for the fortnight before admission.

On admission the urine, which was removed by catheter, contained albumen and blood. There was fever ranging from 99 degrees to 101.2 degrees F.

On 2nd. November the cholesterol content of the blood was 0.089 per cent. On 4th November a suprapubic cystotomy was performed and the bladder was drained. 4 days later the blood findings were:

Cholesterol 0.074 per cent.
Urea 25.2 mgms per 100 c.c.

On November 9th cellulitis appeared over the sacral

region. An incision was made and a large quantity of foul smelling pus was evacuated; a drainage tube was inserted. Later in the day an abscess developed on the left foot; this also was opened. The Patient's condition became steadily worse, no urine being obtained from the suprapubic opening and he died on 14th November, 1922. The temperature had been febrile throughout, but never exceeded 101.2 degrees F.

The post mortem findings were:-

Enlargement of the prostate, acute cystitis, acute ascending pyelonephritis, perinephritic abscess.

CASE IV.

C.Tr. Male, aged 65, was admitted to the Hospital on 1st November, 1921, on account of inability to pass urine, requiring daily catheterisation, of 7 days' duration.

Digital rectal examination revealed the presence of an enlarged prostate. For the rest the physical examination was entirely negative.

On 14th November the cholesterol content of the blood was

0.205 per cent.
Urea Nitrogen 28 mgms per 100 c.c.

8 days later a suprapubic prostatectomy was performed. The patient was discharged 4 weeks after admission, feeling very well.

CASE V.

A.M. Male, aged 62, was admitted to the Hospital on October 1921, on account of difficulty of micturition recurring at intervals after a chill contracted in April 1920.

On admission there was evidence of prostatic enlargement but as the patient was able to pass urine normally surgical interference was not recommended and he was discharged on 1st. November. The cholesterol content of the blood on 20th October 1921 was 0.300 per cent, and the Urea Nitrogen context of the blood was 16.8 mgms per 100 c.c.

He was re-admitted 3 days later on account of acute retention and a suprapubic prostatectomy was performed on 7th November. He was quite well when discharged on 18th November, 1921.

CASE VI.

R.S.,Male, aged 69, a butcher was admitted to the Hospital on 7th., November 1921, complaining of incontinence,of urine with retention of 10 months' duration.

On admission the urine was acid, had a specific gravity of 1012 and contained a trace of albumen. The residual urine amounted to 20 ounces. Digital rectal examination revealed the presence of a large, hard mass on the anterior rectal wall.

On 9th November the blood findings were :-

Cholesterol - 0.270 per cent.
Urea Nitrogen 42 mgms. per 100c.c.

On 14th November a suprapubic cystotomy was performed and the bladder wasdrained. The patient died 8 days later.

The post mortem findings were:

Carcinoma of Prostate with metastases to aortic lymph glands; recent parenchymatous nephritis; old cholecystitis and multiple gall stones; patchy thickening of the mitral and tricuspid valves and coronary atheroma.

CASE. V11.

S.T., Male, aged 78, was admitted to the Hospital on 14th October 1921, on account of pain in the bladder and difficulty of micturition of several months' duration, but worse during the last week. There was evidence of prostatic enlargement.

On October 15 the blood findings were:-

Cholesterol - 0.130 per cent.

Urea Nitrogen 42 mgms. per 100c.c.

Patient refused operation.

CASE V111.

R.H. Male, aged 68, was admitted to the Hospital on account of acute retention of urine. He looked very ill the breathing was laboured and there was frequent hiccoughing.

There was no fever. The urine was neutral, had a specific gravity of 1011, and contained albumen. On October 28th a Suprapubic Cystotomy was performed and the bladder was drained. Several blood urea estimations were made.

3.10.21	Blood	Urea	Nitrogen	56	mgms	per	100c.c.
8.10.21	"	"	"	33.6	"	"	"
20.10.21	"	"	"	16.8	"	"	"
2.11.21	"	"	"	16.8	"	"	"

On Nov. 2nd. blood cholesterol was 0.227 per cent.

The patient was discharged on 14th November 1921, feeling much relieved.

CASE IX.

J.S., Male aged 55 years, was admitted to the Hospital on 31st December 1921, on account of retention of urine and nocturnal dribbling of 11 months' duration.

On admission the bladder was distended; the urine was clear. There was nothing further of note.

On 2nd. January the blood findings were:-

Cholesterol - 0.133 per cent.
Urea Nitrogen 39.2 mgms per cent.

On Jan. 6th a suprapubic cystotomy was performed and the bladder was drained. The patient was sufficiently well to be discharged 4 weeks later and had to attend as out patient.

CASE X.

A.W. Male, aged 74, was admitted to the Hospital on 16th.

February 1922, for retention of urine and incontinence of several months' duration.

On admission he was drowsy and incoherent so that no further history was obtained. There was no fever and the urine was clear.

The cholesterol content of the blood on the day of admission was 0.126 per cent and the urea nitrogen content was 75 mgms per 100 c.c. On the following day a suprapubic cystotomy was performed; a calculus 1" in diameter, of the mulberry oxalate type was found in the bladder and removed. The bladder was drained.

On 23rd February the patient developed a left sided parotitis. On 2nd. March the urea nitrogen content of the blood had risen to 106 mgms per 100c.c The patient became lethargic and complained of shortness of breath and great thirst. He died 4 days later.

The post mortem findings were:-

Prostate: Marked adenomatous enlargement of both lateral lobes.

Urinary bladder: This was greatly hypertrophied and contained numerous small diverticula, in one of which a tiny oxalate stone was found. The mucosa was inflamed.

Kidneys: The capsules were slightly adherent and on stripping these the surface was seen to be finely granular. Several cysts were present and one multilocular abscess of considerable

size, as well as a number of small abscesses.

Heart: The left ventricle was hypertrophied and the coronary arteries were the seat of advanced atheroma.

Aorta. showed slight early atheroma except at the lower end of the abdominal portion where there was a large patch of degenerative, advanced atheroma.

The renal and other smaller arteries showed well marked arterioselerosis.

Adrenals: These were of large size, but cortical lipoid was much reduced.

Lungs: These were markedly emphysematous and there was a gangrenous abscess of the posterior aspect of the right upper lobe as well as a haemorrhagic infarct of the lower lobe.

Knee Joints showed chronic osteo arthritic changes.

CASE XI.

H. W., aged 68. a miner, was admitted to the Hospital on January 10th., 1922, for acute retention of urine. There was nothing of note to be made out on physical examination. On 12th. January a suprapubic cystotomy was performed and the bladder was drained. The blood findings were:- (2 days later)

Cholesterol - 0.092 per cent.
Urea nitrogen 42 mgms per 100c.c.

14 days later the contents of the blood were:-

Cholesterol - 0.108 per cent.
Urea Nitrogen 42 mgms per 100 c.c.

A fortnight still later they were:-

Cholesterol - 0.104 per cent.
Urea Nitrogen 25.2 mgms per 100 c.c.

On the 16th February 1922 the suprapubic opening was enlarged and the prostate removed. The patient was quite well when he was discharged on 18th March.

CASE XII.

E.M., Male, aged 70, was admitted to the Hospital on 24th. December 1921. on account of retention of urine: No further History was obtained.

On 29th December the blood findings were:

Cholesterol - 0.106 per cent.
Urea Nitrogen 79.5 mgms per 100 c.c.

A suprapubic cystotomy was performed on the following day, and the bladder was drained. The patient dies 2 weeks later.

The post mortem findings were:-

Prostate: Benign enlargement, affecting especially the middle lobe.

Bladder and Urethra. are the seat of acute cystitis and urethritis.

Kidneys: There is moderate dilation of the pelvis on both sides, there is a very intense acute pyelitis with purulent

exudate. On the right side the infection has spread to the kidney parenchyma.

Heart:Musculature very flabby.

Adrenals: These are soft and the cortical lipoid is greatly reduced.

Lungs: Purulent Crouchitis and Broncho-Pneumonia with acute abscess of left lower lobe.

CASE XIII.

J. W. Male, aged 71, a forgeman, was admitted to the Hospital, under the care of Sir Berkeley Moynihan, on 21st November 1921, complaining of difficulty of micturition of several years' duration, but worse during the last few days.

On admission he was slightly fevered (99.3 F), but for the rest there was nothing of note. He was operated on the same day, a suprapubic cystotomy being performed. After operation there was slight pyrexia for a few days, the temperature ranging between 99.5 and 100.8 degrees F.

On 25th. November, that is 4 days after the operation the cholesterol content of the blood was 0.173 per cent and the urea nitrogen content was 40 mgm per 100 c.c.

On 15th December the prostate was removed through the suprapubic opening and a drainage tube was inserted. The patient did well and was discharged on 7th. February 1922.

CASE XIV.

J. Rh., aged 60, was admitted to the Hospital, under the care of Mr. Collinson, on 4th., March 1922, complaining of inability to pass urine for the last 3 weeks, during which time he has had to be catherised daily.

Rectal examination revealed the presence of an enlarged prostate. The urine was alkaline, had a specific gravity of 1020 and was free from albumen, blood , pus and sugar.

On 6th. March the blood findings were:

Cholesterol - 0.136 per cent.
Urea Nitrogen 22.4 mgms per 100c.c.

On 8th March a suprapubic prostatectomy was performed, the prostate was not much enlarged, but the middle lobe was prominent. The patient made a good recovery and was discharged on 1st. April 1922.

CASE XV.

W.H., aged 78, was admitted to the Hospital under the care of Mr. Dobson on 6th January, 1922. for acute retention of urine. Patient has had difficulty in passing urine for the last 20 years, but the condition has steadily become worse so that he has to get up about 20 times during the night and only succeeds in passing a little at a time. This is the first time that he has had, complete retention.

On admission the bladder was much distended. Rectal examination revealed the presence of a large hard swelling

on the anterior rectal wall. Haemorrhoids were present. The urine contained albumen and blood; the centrifuged deposit contained numerous cocci and yeast cells. Cultures gave a rich growth of Streptococcus faecalis.

On January 10th, 1922 the blood findings were:-

Cholesterol content - 0.166 per cent.
Urea Nitrogen - 33.6 mgms per 100 c.c.

He was diagnosed as a case of malignant disease of the bladder with enlargement of prostate and was transferred to the Parish Hospital.

CASE XVI.

D.F. aged 49, was admitted to Hospital on November 9th., 1921, on account of Naematuria. He has had difficulty with micturition for the last 6 months. The first attack of naematuria occurred 3 months before admission. He has had 3 such attacks since.

On admission nothing could be made out on physical examination except some enlargement of the prostate. On 21st. November the blood findings were: -

Cholesterol - 0.354 per cent.
Urea Nitrogen 30.8 per 100 c.c.

3 days later a suprapubic cystotomy was performed and a drainage tube inserted. After the operation there was irregular pyrexia, the temperature ranging from 99 - 103 degrees F.

On the 3rd of December the patient suddenly fell back in bed, became comatose and died.

The post mortem findings were:-

Peritoneum: Normal.

Bladder: No evidence of cystitis.

Prostate: Enlarged and seat of benign hyperplasia.

Kidneys: Congested, but otherwise normal.

Lungs: Bilateral empty sema.

Heart: Muscle soft and flabby; patchy thickening of mitral cuspo; slight atheroma of coronary arteries.

Aorta: Advanced atheroma of both thoracic and abdominal portions.

CASE XVll.

I.B. aged 51, was admitted to the Hospital on 7th. December 1921, complaining of slight urinary incontinence and increased frequency of micturition of 8 weeks' duration.

Rectal examination revealed the presence of an enlarged prostate. On cystoscopic examination both ureters were seen to be working normally. Operation was not considered advisable and the patient was discharged on 17th. December.

On 8th. December the blood findings were:-

Cholesterol - 0.196 per cent.
Urea Nitrogen 16.8 mgms per 100 c.c.

CASE XVlll.

J.B. aged 68, was admitted to Hospital complaining of

retention of urine of 3 days' duration on February 4th.,1922.

Digital rectal examination revealed the presence of a hard swelling on the anterior rectal wall. The urine contained albumen, blood and pus. The temperature was normal.

On 6th February the blood findings were:-

Cholesterol - 0.109 per cent.
Urea Nitrogen 75.6 mgms per 100 c.c.

On the same day the bladder was opened and drained. After operation there was irregular pyrexia, the temperature ranging from 99 degrees - 101 degrees F.

On the 3rd. March the patient developed hiccough; the respirations became rapid; coma set in followed by death.

The post mortem findings were:

Prostate: The seat of benign glandular hyperplasia.

Bladder: Acute cystitis.

Kidneys: Intense acute ascending pyelonephritis on both sides.

Arteries: Aortic and coronary atheroma.

Adrinals: Complete disappearance of cortical lipoid.

CASE XIX.

J. S., aged 80, was admitted to the Hospital on 15th January, 1922 with acute retention of urine.

On the same day a suprapubic cystotomy with drainage was performed, under local anaesthesia.

On the day following operation the cholesterol content

of the blood was 0.140 per cent and the urea nitrogen content was 39.2 mgms per 100 c.c.

A fortnight later the cholesterol content of the blood was 0.160 per cent and the urea nitrogen content was 25.2 per 100 c.c.

Patient was discharged on 7th. February, 1922 much relieved.

CASE XX.

J.W., aged 58, admitted to Hospital on 13th. February, 1922 for acute retention of urine.

On 14th February the blood findings were:-

Cholesterol - 0.150 per cent.
Urea Nitrogen 25.2 mgms per 100 c.c.

On 17th February a suprapubic prostatectomy was performed. The patient was discharged on 28th March feeling well.

CASE XXI.

R.B. aged 67, was admitted to Hospital on 6th. February 1922, complaining of pain and difficulty of micturition with passage of blood in the urine of 5 weeks' duration.

Digital Rectal examination revealed the presence of a large mass about the size of a tangerine orange on the anterior rectal wall. The urine contained triplephosphates, but no albumen or other abnormal constituents.

On 7th. February the cholesterol content of the blood was

0.230 per cent and the urea nitrogen content 33.6 mgms per 100 c.c.

On 12th February a suprapubic cystotomy with drainage was perfoemed. There was slight elevation of temperature the following day but the temperature was normal afterwards.

On 20th February the blood findings were:-

Cholesterol - 0.113 per cent.
Urea Nitrogen 30 mgms per 100 c.c.

On 9th. March the bladder was re-opened with the object of removing the prostate, but a large inoperable carcinoma was found at the base.

On 17th. March the cholesterol content of the blood 0.176 per cent. The patient was transferred to the Parish Hospital on the 24th. March.

CASE XXII.

C.C.T., aged 56, was admitted to the Hospital on 29th. January 1922 on account of difficulty with micturition of three months' duration.

On the following day the blood findings were:-

Cholesterol - 0.133 per dent.
Urea Nitrogen - 16.8 mgms per 100 c.c.

Prostatectomy was performed on 2nd. February. There was slight fever for a fortnight after the operation, the temperature ranging from 99 degrees - 102 degrees F.

On 14th. February the blood findings were:-

The Cholesterol - 0.093 per cent.
Urea Nitrogen - 30.8 mgms per 100 c.c.

The patient was discharged 3rd. March much improved.

CASE XXIII.

S. Br., aged 66 was admitted to the Hospital on 8th. February 1922 on account of stoppage of the bowels. In April 1920 the patient had diarrhoea, and this lasted for 28 weeks. The motions were fluid, offensive and blood stained. The condition gradually improved and the diarrhoea ceased altogether five weeks before admission. A fortnight before admission he began to have pain on micturition and noticed blood in the urine. At the same time the bowels ceased to act.

On admission he was seen to be markedly emaciated and he was delirious. There was visible intestinal peristalsis, the liver was not enlarged and there was no glandular enlargement. Per rectum a hard swelling was felt on the anterior rectal wall; it was very tender and its upper limit could not be defined. There was marked fever, the temperature ranging from 100 to 102.2 degrees F. The urine contained albumen, blood and pus. The bowels moved regularly while in hospital. A diagnosis of carcinoma Ventriculi and Malignant Prostate was made.

On 11th. February the blood findings were:-

Cholesterol - 0.070 per cent.
Urea Nitrogen - 30.8 mgms per 100 c.c.

The patient dies on 1st March.

The post mortem findings were:-

Lungs: Old healed tubercle.

Heart: Atheromatous calcareous deposits on aortic valves.

Aorta: Moderate patchy atheroma.

Kidneys: Left kidney shows marked inflammation of pelvis, with small abscess.

Right Kidney: retention cysts.

Adrenals: Cortical lipoid much reduced.

Bowel & Bladder: Intestines matted together; plastic peritonitis; ulcerating carcinoma at upper end of rectum. Fistulous communication with ileum and with posterior wall of bladder from rectum.

VI (C) RENAL, VESICAL AND URETHRAL CONDITIONS.

CASE I.

F.H., male, aged 39, a butcher's assistant, was admitted to the Hospital on the 20th. February 1922. complaining of difficulty in passing urine. A bougie was passed and a stricture was diagnosed.

On 21st. February the blood findings were:-

Cholesterol - 0.190 per cent.
Urea Nitrogen - 25.2 mgms per 100 c.c

The stricture was dilated and patient was discharged to attend the out patient department.

CASE II.

M.Tr., male, aged 64, was admitted to the Hospital on 22nd. February 1922. complaining of slight urinary incontinence. This has been in existence for the last five years. It became so troublesome in March 1918 that he had to undergo an operation at the Manchester Royal Infirmary. He remained free of symptoms for nine months when they again returned. There was a history of gonorrhoea 25 years ago.

The urine was clear. A bougie was passed and the stricture was dilated. The patient was transferred to the out patient department.

On the 24th. February 1922 the blood findings were:-

Cholesterol - 0.160 per cent.
Urea Nitrogen 25.2 mgms per 100 c.c.

CASE 111.

H. Th., male, aged 43, was admitted to the Hospital on 7th. March 1922, on account of pain on micturition of 9 months' duration.

Patient suffered from nocturnal incontinence of urine till the age of 16. From that time until April 1921 he had no trouble with micturition.

There was no history of Syphilis or gonorrhoea. The physical examination was entirely negative. The urine was turbid, alkaline and contained albumen, blood and pus.

On 7th March the Blood findings were:-

Cholesterol - 0.150 per cent.
Urea Nitrogen - 33. 6 mgms per 100 c.c.

9th. March showed that the bladder and prostate were inflamed. The bladder was washed out and the patient was discharged on 15th March.

CASE IV.

Th.M., male, aged 64, was admitted to the Hospital on 21st January, 1922, complaining of difficulty and increased frequency of micturition with pain during the act, of 2 years' duration. The symptoms have gradually become worse Blood in urine was first noticed 1 year ago. Patient has lost flesh. On admission patient was seen to be a markedly

emaciated man. Digital rectal examination revealed the presence of a large hard mass on the right lateral wall of the rectum. The urine contained a trace of albumen. For the rest there was nothing of note. On 24th January the cholesterol content of the blood was 0.210 per cent, and the urea nitrogen content was 22.4 mgms per 100 c.c.

On 2nd. Febraary a suprapubic incision was made, the peritoneum reflected and the bladder examined. A large, fixed growth was found on the superior surface.

The condition was considered inoperable and the abdomen was closed. The patient was transferred to the Parish Hospital, on 11th February.

CASE V.

S.T.J., male, aged 40, was admitted to the Hospital on 21st. November 1921, complaining of difficulty in passing of urine 2 years' duration, with pain over the bladder region of 2 weeks' duration. He has noticed a swelling over the left testicle for the last 12 months, He attributes it to an injury which he received 2 years ago. There is a history of gonhorrhoea - contracted 14 years ago.

On admission the left testicle was found much enlarged, with swelling of the epididymis. Per rectum enlargement of the prostate could be made out.

On 22nd. November the blood findings were:-

Cholesterol - 0.177 per cent.
Urea Nitrogen 16.8 mgms per 100 c.c.

On 24th November the testicle was removed and the urethral stricture was dilated. The testicle was found on examination to be tubercular.

CASE VI.

F.K., male, aged 44, was admitted to the Hospital on 24th October 1921, complaining of pain on micturition Patient had a fall in July 1918 and sustained various injuries, among others fracture of the spine in the lower lumbar region. As a result of this he became paralysed, suffered from loss of sensation in the lower limbs and from incontinence of urine and faeces. Four months afterwards he regained control over the bladder and at the end of 1918 he recovered the use of the right leg. At the beginning of 1919 he began to have rigors, these being preceded by frequency of micturition and incontinence. He was treated with Quinine and later received a vaccine and the condition improved. He is now able to pass urine normally, but has scalding pain in the perineum during the act.

On admission there was evidence of an old paraplegia. The urine was alkaline, had a specific gravity of 1015, and contained pus. X Ray examination revealed the presence of 2 calculi in the bladder.

On 25th October the blood findings were:-

Cholesterol - 0.200
Urea Nitrogen - 19.6 mgms per 100 c.c.

On 31st. October a suprapubic Lithotomy was performed and drainage provided for. Patient was discharged on 26th November, feeling well.

CASE VII.

C.B. Female, aged 57, was admitted to the Hospital on 7th. December 1921, complaining of frequency of micturition and pain in the left side of 3 years' duration. X ray examination revealed the presence of a calculus at the lower end of the left ureter. The urine was negative. On 8th December the cholesterol content of the blood was 0.199 per cent, and the urea nitrogen content was 16.8 mgms per 100 c.c.

On 15th December, under ether anaesthesia, the patient was cystoscoped; a stone was seen impacted at the lower end of the left ureter; the left ureteral onfice was incised, but the stone could not be removed. Patient was discharged 21stl January, feeling much relieved.

CASE VIII.

M.S. Female., aged 51, was admitted to the Hospital on 19th December, 1921, complaining of severe colicky pain in the left side of one month's duration. The pain was so severe that patient was given morphia several times.

8 years ago patient became very thin and began to have dragging pain in the back and at the sides. She was fitted

with a double kidney support and this relieved the symptoms. She remained fairly well until the outset of the present illness.

On admission patient was seen to be a thin, pale and nervous woman. The kidneys could not be felt and X Ray examination was negative. On 20th. December the blood findings were:-

Cholesterol - 0.222 per cent.
Urea Nitrogen - 22.4 mgms per 100 c.c.

Patient was discharged on 30.th. December, feeling much better.

CASE XIX.

K.W., Female, aged 42, was admitted on 30th. November 1921, complaining of paroxysmal attacks of severe pains in the lower abdomen accompanied by the passage of blood stained urine of 3 weeks' duration.

On admission the abdomen was seen to be full and on palpation a tense cystic swelling could be felt on the left side extending from the subcostal margin to the inguinal region. X ray examination was negative. The urine contained blood for the first 6 days, but cleared up subsequently. On 21st December the cholesterol content of the blood was 0.207 per cent and the urea nitrogen content was 33.6 mgms per 100 c.c.

Patient was kept in bed, on a light diet and felt much better when whe was discharged 31st. December.

CASEXX.

J.D. Female, aged 36, was admitted to the Hospital on 7th January 1922, complaining of pain in the left lumbar region of 2½ years' duration.

On admission, except for some tenderness in the left lumbar region, there was nothing abnormal to be made out. X ray examination was negative. The urine containing albumen and pus. Scanty staphylococci were recovered in cultures. There was no fever. Cystoscopy showed that both ureters were working normally.

On 10thn, January the blood findings were:-

Cholesterol - 0.120 per cent.
Urea Nitrogen - 22.4 mgms per 100 c.c.

The case was diangnosed as one Pyelitis and the patient was kept on a light diet and received dieuretic mixtures She was improved when discharged on 17th January.

CASE XI.

S.M. Male, aged 17, was admitted to the Hospital on 25th October, 1921 on account of the passage of blood stained urine of several weeks' duration.

On admission urine contained albumen, blood and pus. There was also slight fever, the temperature ranging from 98.8 to 99.5 degrees F. For the rest, there was nothing

of note. On 31st October the blood findings were:-

Cholesterol - 0.131 per cent.
Urea Nitrogen - 22.4 mgms per 100 c.c.

Patient was discharged on 17th November, improved.

CASE XII;

J.H. Male, aged 57, was admitted to the Hospital on 6th November, 1921 with symptoms of uræmia. No further history was obtained. The urine on admission contained albumen and hyaline casts.

On 8th November the blood Cholesterol content was 0.283 per cent. Patient was treated with diurectics and diaphosetics and his condition improved.

On 7th December 1921 the cholesterol content of the blood was again determined and was found to be 0.266 per cent

The urea nitrogen content of the blood was not determined.

CASE XIII.

M.M. Female, aged 43, was admitted to the Hospital on 19th November 1921, on account of convulsions, the first of which occurred 5 days prior to admission.

The patient had not been well for 2 years, but had no definite symptoms. 10 days before admission headaches became troublesome and 5 days later she had a convulsion. She had another convulsion on the night of admission. She was admitted in a comatose condition at 2 a.m. on 19th November. She died the following day.

The cholesterol content of the blood on 19th November that is on the day preceding death was 0.242 per cent.

The post mortem findings were:-

Kidneys: Atrophied, capsule thickened and adherent; the surface very coarsely granular - extreme interstitial nephritis.

Heart: Hypertrophied left ventricle, coronary atheroma.

Lungs: Hypostatic congestion of lower lobes, oedema of the rest of the lungs.

There was nothing further of note.

CASE XIV.

W.Y. Male, aged 55, a private patient, had marked symptoms and physical signs of arteriosclerosis. The systolic blood pressure was 250 m.m. of Mercury. The cholesterol content of the blood was 0.259 per cent

CASE XV.

F.N. Male, aged 14, was admitted to Hospital on 24th January 1922, with a history of recurrent attacks of swelling of the body since August 1921.

He was in bed for 5 weeks in August and September 1921, and apparently was quite well until December 1921, when the swelling recurred.

On admission there was oedema of the feet and slight oedema of the subcutaneous tissues of the back. The urine contained much albumen; no casts were found. The fundi oculi were normal.

On 7th. February a blood examination was made. There was marked lipaemia. The cholesterol content of the blood was 0.430 per cent.

CASE XVI:

Th. D. Male, aged 54, was admitted to Hospital on 31st. January 1922, complaining of pain in left lumbar region of 12 Months' duration, with swelling of 3 months' duration.

On admission there was marked fulness in the left hypochondriac region., and in the flank and a large tumour could be felt. On the 7th. February the cholesterol content of the blood plasma was 0.157 per cent.

A. Nephrectomy was performed, the tumour proved to be a hypernephromen. Patient was feeling well when discharged on March 8th, 1922.

VII (A) ANAEMIA, PRIMARY AND SECONDARY.

CASE 1.

A.S. Male, aged 53, was admitted to Hospital on 25th October, 1921 complaining of vomiting of blood of 3 days' duration. Patient has suffered from indigestion for the last 18 months, since when he has had pain in the epigastric region coming on shortly after food, and relieved by vomiting The stools have sometimes been dark in colour but there has been no previous vomiting of blood.

On admission patient was seen to be a spare pale man. There was no more vomiting, but the stools were found to contain occult blood. There was marked rigidity with tenderness in the abdomen, the tenderness being localised to a point in the middle line, midway between the umbilicus and xiphoid.

On 28th. October the blood findings were:-

Cholesterol 0.157 per cent.
Haemoglobin 45 per cent.
Colour Index 0.73
White Cells 4,800
Differential Count:
Polymorphs: Neutrophil 54.5 per cent.
" Eosinophil 7.5 " "
" Basophil 0.1 " "

Large mononuclears: 4.2 per cent.
Lymphocytes 33.7.

The films showed some variation in the sign and shape of the reds with scanta nucleated reds.

The Patient was transferred to the Surgeon as a case of

gastric ulcer.

CASE II.

J.H., male, aged 5, attended the out-Patient Department on account of listlessness, loss of appetite and pallor of several months' duration.

Patient was an undersized, pale and thin boy, with a prominent abdomen. The spleen could just be felt; for the rest there was nothing of note.

On February 14th. the blood findings were:-

Cholesterol - 0.120
Erthyocytes: 3,900,000.
Haemoglobin: 40 per cent.
Colour index: 0.5.
Leucocytes: 6,000

Differential Count:

Polymorphs: Neutrophil 63.5 per cent.
" Eosinophil 2.0. "
" Basophil 0.5 "

Large Mononuclears: 6.0. per cent.
Lymphocytes: 28.0 "

CASE III.

J.B. Male, aged 45, was admitted to Hospital on 12th February, 1922, complaining of weakness and lassitude with loss of flesh of 4 months' duration.

On admission he was seen to be a spare, pale man. There was marked pulsation in the vessels of the neck and in the epigastrium. Cardiac examination was negative. There was nothing further of note.

On 17th February the blood findings were:-

Cholesterol plasma 0.128 per cent.
Corpuscles 0.082 " "
Erythrocytes 2,800,000 " "
Haemoglobin 50 per cent.
Leucocytes 3,800

The red cells were well formed and were regular in their staining reactions. No nucleated reds were seen.

Patient recovered under treatment with Iron and Arsenic.

CASE IV.

Mrs. A.S., aged 33, was admitted to hospital on 7th January, 1922 complaining of general weakness and lassitude of 8 weeks' duration. She was confined 6 weeks before admission, but had not felt well for two weeks prior to the confinement. After delivery she remained in bed for 11 days, but felt so weak that she could hardly walk. She was also sick, and this was very persistent. She sought medical advice on account of the weakness and constant vomiting and was admitted to the Infirmary. She gave a history of menorrhagia of several years' duration.

The family history was entirely negative. Patient's children, including the baby aged 6 weeks were well.

On admission patient was seen to be a pale thin woman and very tired looking. The upper teeth had all been removed, the lower were good. The examination of the abdomen and chest was negative. Vaginal examination revealed

a super-involution of the uterus and endocervicitis with erosion.

On 10th January the blood findings were:-

Cholesterol - 0.090 per cent.
Erythrocytes 2,000,000.
Haemoglobin 25 per cent.
Colour Index 0.6.
Leucocytes 4,200.

The films showed marked variation in the size and shape of the red cells, with irregular and polychromatophilic staining.

Patient was treated with Iron and Arsenic and improved, so that on 24th January the blood findings were:-

Erythrocytes 2,800,000
Haemoglobin 50 per cent.
Colour Index 0.9.
Leucocytes 5,600.

The films showed irregularity in the staining and size of the red cells.

CASE V.

Mrs E.T. aged 35, was admitted to the Hospital on 12th November, 1921, complaining of weariness and prostration of several months' duration. Patient was delivered of her 4th child 8 months before admission. She did not feel well, but suckled the infant, as her husband was not working and the child continued on the breast until 2 weeks before admission, when patient collapsed.

On admission she was seen to be a fairly well developed,

but poorly nourished woman; the skin had a lemon tint She looked very ill, answered questions with an effort and voice sounded weak and tired. The pulse was of small amplitude and rapid, 118 per minute. There was no fever Examination of the heart revealed the presence of haemic murmur. There was a Bruit de Diable in the veins of the neck. For the rest there was nothing of note.

On 14th November the blood findings were:-

Cholesterol in plasma 0.103. per cent.
" " Corpuscles 0.119 " "
Erythrocytes 980,000
Haemoglobin 18 per cent.
Colour Index 0.9
Leucocytes 3,300

Differential Count.
Myelocytes 0.5 per cent.
Polymorphs Neutrophil 68.0
" Eosinophil 0.5.
" Basophil 0.5

Large Mononuclears 2.5
Lymphocytes 28.0
Nucleated reds 80 per 100 whites.

Film showed marked anisocytosis and poikilocytosis with polychromatophilia and punctate.

Casophilia. All varieties of nucleated reds were seen including megaloblasto.

Three months later the blood findings were:

Cholesterol in plasma 0.122 per cent.
Erythrocytes: 4.800,000
Haemoglobin: 75 per cent.
Colour Index 0.75.

Patients condition was much improved.

CASE VI:

Mrs. A.M., aged 49, was admitted to Hospital on 15th November 1921, complaining of a swelling in the left side of the abdomen of 2 years' duration. This was her third admission to Hospital, and on her previous stay in hospital she was told that she had an enlarged spleen.

On admission the spleen was considerably enlarged and was found to extend a hand's breadth below the costal margin and to within 2" of the mid-line. The notch could be felt distinctly. The Wassermann reaction was positive and the size of the spleen became reduced under anti-syphilitic treatment.

On 18th November the blood findings were:-

Cholesterol 0.175 per cent.
Blood and Differential Count.

Red Cells 3,900,000.
Haemoglobin 35%
Colour Index 0.47
Leucocytes 2,500
Polymosphs: Neutrophil 73.0 per cent.
" Eosinophil 4.0 "
Basophil -
Large Mononuclears 5.0.
Lymphocytes 21.0.

There was slight variation in the size and shape of the red cells; no nucleated reds were seen.

CASE VII.

A.W., female, aged 34, was admitted to Hospital on the

19th October, 1921 complaining of diarrhoea of several months' duration. This was of sudden onset and after two weeks patient became absolutely exhausted and had to go to bed, where she remained for 4 months.

On admission she was seen to be a pale thin woman. There was visible pulsation in the vessels of the neck and in the epigastrium. There was a soft haemic murmur, the spleen could not be felt. Nothing further of note was made out.

On 23rd. November the blood findings were:-

Cholesterol in plasma 0.107 per cent.
" " Corpuscles 0.070 "

Blood and differential Count.

Erythrocytes 1,800,000.
Haemoglobin 35%
Colour Index 1.0
Leucocytes 2,600
Polymosphs: Neutrophil 55.0 per cent.
" Eosinophil 2.0.
" Basophil 1.0

Lymphocytes 22.0.

There was marked poikilocytosis with anisocytosis and many nucleated reds were seen.

On 21st February 1922 the blood findings were:-

Cholesterol in plasma 0.090 per cent.

Blood and Differential Count.

Erythrocytes 1,000,000
Haemoglobin 20%
Colour Index 1.0.
Polymosphs: Neutrophil 67.0%
" Eosinophil 1.6%
" Basophil -

Large Mononuclears 4.0.
Lymphocytes 27.4

There was marked poikilocytosis with anisocytosis and nucleated reds, including megaloblage were numerous.

CASE VIII.

A.M., female, aged 30, was admitted to Hospital on 9th January 1922. complaining of weakness and loss of appetite since September 1920. There has been improvement with relapses since. In December 1921 she had a very bad relapse and was admitted to Hospital in January on that account.

On admission she was seen to be of a lemon yellow colour and thin. She looked very ill and spoke in monosyllables. The teeth were cavious.

There was a soft haemic murmur, also a bruit de diable over the veins in the neck. For the rest there was nothing of note.

On 10th January the blood findings were:-

Cholesterol 0.070 per cent.
Erythrocytes 800,000
Haemoglobin 15%
Colour Index 0.9
Leucocytes 2,800
Polymosphs: Neutrophil 65.0
" Eosinophil -
Basophil -
Large Mononuclears 4.0
Lymphocytes 28.0
Myclosytes 3.0

Patient died 12 days later and the post mortem findings

were:-

Erythroblastic reaction of the bone marrow:

Fatty degeneration of the heart and liver;

Haemosiderin deposits in liver and spleen.

CASE IX;

A.F. Female, aged 38, was admitted to Hospital on 14th January, 1922 complaining of lassitude and shortness of breath following on an attack of Influenza 3 years previously. Since then there have been improvements and relapses.

On admission she was seen to be a pale, but fairly well nourished woman. The teeth were septic and carious. There was nothing further of note.

On 17th January the blood findings were:-

Cholesterol in plasma 0.080 per cent.
" Corpuscles 0.140 "
Erythrocytes: 2,400,000
Haemoglobin: 50 %
Colour Index: 1.0.
Leucocytes: 5,600.
Polymosphs: Neutrophil 62.5%
" Eosinophil 2.0
" Basophil 2.5
Large Mononuclears 2.5.
Lymphocytes 32.5

The red cells, showed some variation in size and shape.

CASE X.

M.M., Male, aged 48, was admitted to hospital on 23rd., January 1922. complaining of weakness and shortness of breath of 1 year's duration. He has been unable to work and has

lost a stone in weight since the outset of the illness.

On admission he was seen to be a well developed and fairly well nourished man, but pale. The teeth were decayed and there was marked pyorrhoea alveolaris. For the rest there was nothing of note.

On 30th January 1922, the blood findings were:-

Cholesterol in plasma - 0.132 per cent.
" in Corpuscles 0.117 "
Erythrocytes: 2,700,000
Haemoglobin: 55%
Colour Index: 1.1
Leucocytes 6.400

Apart from variation in size and inequality of staining of the red cells there was nothing of note.

CASE II.

J.S., male, aged 54, was admitted to Hospital on 23rd. February 1922, complaining of weakness and shortness of breath of 8 months' duration. Patient stated that he was quite well until May 1921 when he met with an accident in the pit - pinned down by a fallen roof. He was able to get up when he was released but complained of pain in the back and left side and has been unable to work since. He has become pale and has lost flesh.

On admission he was seen to be a muscular individual, but thin and of a lemon yellow colour. The teeth were badly decayed. For the rest the physical examination was entirely

negative.

On the 27th February the blood findings were:-

Cholesterol in plasma 0.072 per cent.
Erythrocytes 900,000
Haemoglobin 20%
Colour Index 1.1.
Leucocytes: 3,000.

There was marked poikilocytosis with anisocytosis, polychromato, philia and punctate basophilia. Nucleated reds, including megaloblasts were present.

CASE XII.

E.P. Male, aged 33, was admitted to Hospital on 14th. February complaining of palpitation, shortness of breath on exertion and mental depression of,10 months' duration.

On admission he was seen to be a well developed and fairly well nourished man, but pale. The respiratory and alimentary systems appeared to be normal.

Both knee jerks were exaggerated, there was a bilateral Babinski and ankle clouns could be elicited. The examination of the heart was negative. There was nothing further of note.

On 15th. February the blood findings were:-

Cholesterol in plasma 0.131 per cent.
" " Corpuscles 0.081 "
Red Cells 2,200,000.
Haemoglobin 40%.
Colour Index 1.0.
White cells 5.500%
Polymosphs: Neutrophil 58.7.
: eosinophil 1.0.
basophil -

Large Mononuclears 2.0.
Lymphocytes 38.0.

There was marked anisocytosis with poikilocytosis, polychromatophilia and punctate basophilia. A few nucleated reds were seen.

On 9th March 1922, the blood findings were:-

Cholesterol in plasma 0.110.
" " Corpuscles 0.077.
Red Cells : 3,400,000
Haemoglobin 68%
Colour Index 1.1.
White Cells 5,200.
Polymosphs: Neutrophil 53.5%
: Eosinophil 4.0%
: Basophil 0.5%
Large mononuclears 4.0%
Lymphocytes 38.0%

There was slight variation in the size and shape of the cells, but nothing else of note. Although there was a marked improvement in the blood count, the patient's general condition appeared to be worse.

The appetite was worse and he was much more depressed.

VII (b) CASES ASSOCIATED WITH SPLENOMEGALY ARE CASES (1 - 5) OF LEUCAEMIA.

CASE I.

Mrs. M.W., aged 35, was admitted to hospital on 21st November, 1922 complaining of pain in the left side of the abdomen when lifting heavy weights, of 12 months' duration. She has lost flesh and has had attacks of diarrhoea during the last 7 weeks. One week before admission she had an

attack of epistaxis.

On admission patient was seen to be a pale, thin woman, with a somewhat prominent abdomen. The spleen was much enlarged the lower edge extended 2" below the level of the Umbilicus. The notch could be felt. There was some tenderness. For the rest physical examination was negative.

On 8th. December the blood findings were:

Cholesterol in plasma 0.104 per cent.
Erythrocytes: 3,200,000.
Haemoglobin: 40.
Colour Index: 0.6.
Leucocytes: 210,000.

Differential Count (600 Whites).
Non granular cells (Myeloblasts) 7.0%
Myelocytes: Neutrophil 44.0.
: Eosinophil 3.8.
: Basophil 7.2.
Polymorphs: Neutrophil 34.0.
: Eosinophil 2.8
Lymphocytes 1.2

Numerous nucleated red cells present.

CASE II.

J.B., Male, aged 57, was admitted to Hospital on 12th. December, 1921, complaining of a feeling of tightness in the abdomen with pain in the left side, of several months' duration. There was no history of haemorrhage.

On admission the spleen was found to be greatly enlarged extending to 1 inch below the level of the umbilicus. There was tenderness especially along the anterior margin. No

friction sounds were audible. For the rest the physical examination was negative.

On 16th December the blood findings were:-

Cholesterol in plasma: 0.127 per cent.
Erythrocytes: 5,100,000
Haemoglobin: 70%.
Colour Index: 0.77.
Leucocytes: 220,000
Non granular cells (Myeloblasts) 5.5%.
Myelocytes: Neutrophil 31.4%.
: Eosinophil 0.3%
Polymorphs: Neutrophil 57.1.
: Eosinophil 2.0%
: Basophil 2.3%
Lymphocytes 1.4%
One nucleated red was seen.

On 31st January 1922, after patient had been under X ray treatment for 6 weeks and the size of the spleen had been reduced, the blood findings were:-

Cholesterol in plasma: 0.109 per cent.
Erythrocytes: 5,000,000.
Haemoglobin: 60%
Colour Index 0.6
Leucocytes: 10,000.

Differential Count.

Polymosphs: Neutrophil: 55.0%
: Eosinophil: 4.0.
: Basophil: -
Large hylaine cells: 3.0.
Myclocytes: Eosinophil: 5.0.
: Neutrophil: 8.0.
: Basophil: 15.0.

CASE III.

W.W.J., Male, aged 67, was admitted to Hospital on 10th October 1921, complaining of abdominal swelling with discolouration of the skin of 6 months' duration. An enlarged

gland in right axilla has been noted for the last 5 years but it has become bigger of late. Enlarged submaxillary glands were first noticed 18 months before admission.

On admission patient was seen to be a thin, pale man, with a slight icteric tinge about the sclerotics and the face . There were enlarged glands in both axilla, groins and submaxillary regions. The spleen was enlarged, its lower edge being a hand's breadth below the subcostal margin. The liver was palpable 1 finger's breadth below costal margin, there was a haemic murmur.

On 11th October 1921 the blood findings were:-

Cholesterol in plasma - 0.108 per cent.
Erythrocytes: 2,800,000.
Haemoglobin: 20.
Colour Index: 0.4
Leucocytes: 900,000.

The white cells were almost all lymphocytes of the type met with in chronic lymphatic leucaemia.

Patient died two months later.

CASE IV.

Th. W., Male, aged 55, was admitted to Hospital on 31st January, 1922, complaining of pain in the left side of 6 months' duration. He has had several attacks of of vomiting and epistaxis.

The spleen, on admersion, was found to be much enlarged the lower edge extending to the anterior superior iliac spine, the notch was felt at the level of the umbilicus.

There was slight oedema of legs. Pyorrhoea alveolaris was very marked. There was no fever.

On 7th March the blood findings were:

Cholesterol in plasma 0.099 per cent.
Erythrocytes: 4,500,000
Haemoglobin: 55%
Colour Index: 0.66
Leucocytes: 265,000

The film shows numerous myelocytes - typical of myloid leucaemia. Numerous Nucleated red cells were seen.

CASE V.

W.A. male, Aged 56, was admitted to Hospital on 8th. October 1921, complaining of weakness, loss of flesh and abdominal pain of six months duration.

On admission the spleen was found to be considerably enlarged, the lower border extending to the level of the umbilicus. For the rest there was nothing of note. The temperature was normal.

On 10th October the blood findings were:-

Cholesterol in plasma:	0.090 per cent.
Erythocytes:	4,000,000
Haemoglobin:	45
Colour Index:	0.56
Leucocytes:	110,000

The films showed numerous myelocytes - typical myeloid leucaemia. Numerous nucleated red cells were seen.

6 - 9 ARE CASES OF ACHOLURIC FAMILY JAUNDICE.

CASE 6.

Mrs. B. age 28, a nurse was admitted to Hospital on 12th.

January, 1922, complaining of recurrent attacks of jaundice with abdominal pain since the age of 19. Patient's father had similar affection 18 years ago. Patient has always had a sallow complexion. Since the age of 19 she has had repeated attacks of jaundice. Two years ago enlargement of the spleen was noticed. She was treated as a case of Splenic Anaemia, receiving 5 applications of X rays to the spleen and injections of arsenic and strychnine. No improvement resulted from this treatment. The spleen has become much enlarged during the last month. Patient has lost two stones in weight in three years. The motions have never been clay coloured.

On admission the patient was seen to be fairly well developed, but thin woman, with a definite icteric tinge of the sclerotics and the whole skin. The spleen was much enlarged; the notch was at the level of the umbilicus and the lower border could be felt 2" below the umbilicus. There was tenderness over the notch. The liver could not be felt. Temperature 100 degrees F. Pulse 108. Respirations 21. The urine contained urobilin, but no bilirubim. The stools were cholic. On 19th January 1922 the blood findings were:-

Cholesterol in plasma:	0.094%
Erythrocytes:	2,600,000
Haemoglobin:	40%
Colour Index:	0.8
Leucocytes:-	3,800
Polymorphs: Neutrophil:	60.4
Eosinophil:	0.6
Large mononuclears:	5.2
Lymphocytes:	33.8

The films showed marked anisocytosis and poikilocy-tosis with polychromato philia and punctate basophilia. Scanty normoblasts were seen.

Patient had irregular pyrexia with rigors and became deeply jaundiced. On 28th. January a blood transfusion was performed; ¾ pint of blood being transfused.

She continued having rigors and looked ill.

13 days after the transfusion the blood findings were:-

Cholesterol in plasma:	0.126 per cent
" " corpuscels:	0.102 " "
Erythrocytes:	3000,000
Haemoglobin:	45%
Colour Index:	0.75
Leucocytes:	7,400

FRAGILITY OF RED CELLS.

Initial haemolysis in % saline.	Complete haemolysis in % saline.
0.500	0.425

10 days later 20.222 three hours after a rigor.

0.525	0.500

On 23rd. February 600 c.c. of blood were transfused directly from a case of Polycythaemia Vera.

The blood findings the following day, just before operation, were:-

Cholesterol in plasma:	0.200 per cent.
" " corpuscles:	0.086 " "
Erythrocytes:	4,500.000
Haemoglobin:	60%
Colour Index:	0.7
Leucocytes:	12,000.

	Initial Haemolysis in % Saline.	Complete Haemolysis. in % saline.
2 hours before operation.	0.500	0.450.
Blood from splenic vein.	0.725	0.525.

On 24th. January splenectomy was performed. The gall bladder was found to be enlarged and full of stones, but the patient's condition did not permit of their removal at this stage.

A marked improvement in the patient's condition occurred almost immediately after the operation. The jaundice disappeared completely 3 days after the operation. 14 days later urobilin could not be detected in the urine, and the patient felt remarkably well.

10 days after operation the blood findings were:-

Cholesterol in plasma:	0.162 per cent
" " corpuscles:	0.080 " "

Initial haemolysis in % saline.	Complete haemolysis in % saline.
0.650	0.525

19 days after operation the blood findings were:

Cholesterol in plasma:	0.200%) Duplicate 0.198%)
" " corpuscles	0.102 per cent.

Patient was discharged a week afterwards. She was seen in the out-patient Department 24 days after the operation, when she looked and felt extremely well. The blood findings were:

Cholesterol in plasma:	0.222%
" " corpuscles	0.107%

Initial haemolysis in % saline	Complete haemolysis in % saline.
0.625	0.450

CASE VII.

J.W. male, aged 60, the father of Mrs. B. (case 6) had a similar affection to that described above 18 years ago. He was seen whilst visiting his daughter. He, too, had an icteric tinge about the scherotics and face. Blood examination revealed an increased fragility of erythrocytes, characteristic of acholuric family jaundice, and a low cholesterol content of the blood, thus:-

Cholesterol in plasma:	0.097 per cent.
" " Corpuscles:	0.077 " "

Fragility of red cells.

Initial haemolysis in % saline.	Complete haemolysis in % saline.
0.650	0.550

CASE VIII

S.G. female, aged 28, a nurse, was admitted to hospital on 20th. January, 1922, complaining of jaundice since birth,

and attacks of pain with rigors, followed by deepening of the jaundice of 7 years duration.

Patient's mother was said to have been slightly jaundiced all her life and died at the age of 24 of supposed Pernicious Anaemia.

Patient herself has been jaundiced all her life. In 1915 she began to have the attacks described above. In 1916 she had cholecystotomy performed and 300 small gall stones were removed. Her condition did not improve, and one month later a cholecystenterostomy was performed. This, too, did not bring about any improvement. During the next 2 years (1917-1918) the jaundice became worse, and she had six severe attacks of rigors, pain and deepening jaundice. In 1918 the opening into the duodenum was enlarged, but patient's condition became worse.

On admission to hospital in January 1922 she was seen to be a well nourished woman deeply jaundiced. The spleen was much enlarged, extending to within 2" of the anterior superior spine below, and to the middle line anteriorly. The notch could be felt just above the umbilicus. There was tenderness all over the spleen. The urine was acholic and the stools were cholic. The Warsermerin reaction was negative. On 23rd. January the blood findings were:-

Cholesterol in plasma:	0.112%
" " corpuscles:	0.105%
Erythrocytes:	3,000,000

Haemoglobin : 40%
Colour Index: 0.6
Leucocytes: 6,400

9 days later the blood findings were:-

Cholesterol in plasma: 0.104 per cent.
" " corpuscles: 0.110 " "

FRAGILITY OF RED CELLS

Initial haemolysis in % of saline	Complete haemolysis in % saline
0. 550	0.500

On 3rd. February splenectomy was performed.)The (blood blood findings/obtained from splenic vein) were:-

Cholesterol in plasma: 0.105%
" "

Initial haemolysis in % saline	Complete haemolysis in % saline.
0.725	0.625

1 week after splenectomy the blood findings were:-

Cholsterol in plasma: 0.109 %
" " corpuscles: 0.090 %

Initial haemolysis in % saline.	Complete haemolysis. in % saline.
0.550	0.500

3 weeks after splenectomy the blood findings were:-

Cholesterol in plasma: 0.171 %
" " corpuscles 0.108 %

6 weeks after splenectomy the blood findings were:

Cholesterol in plasma: 0.197 %
" "corpuscles: 0.108 %
Erythrocytes: 5,000,000.
Haemoglobin: 68 %.

Colour Index: 0.68
Leucocytes: 9,800

After splenectomy the jaundice disappeared entirely. Urobilin which was present in the urine, could not be detected. The blood plasma which had contained bilioubin, was free from bile pigments. Patient felt remarkably well when she was discharged on 4th. March 1922.

She was seen in the out-patient department 11 weeks after the operation, when the blood findings were:-

Cholesterol in plasma: 0.234 %
" corpuscles: 0.119 %

Erythrocytes: 5,800,000
Haemoglobin: 80%
Colour Index: 0.7

CASE IX

H.J.C. male, aged 20 was admitted to hospital on 31st. August 1921 on account of pain in the abdomen 3 months duration, and jaundice since the age of 3. He was in hospital 10 years ago with the same complaint. The family history was negative.

On admission the patient was seen to be a fairly well nourished youth, quite definitely jaundiced. The spleen was much enlarged and at operation weighed 57 ounces.

The stools were cholic, the urine was acholic and contained urobilin.

The fragility of the red cells was increased.

On 14th. October 1921 the blood findings were:-

Cholesterol in plasma:	0.060 %
Erythrocytes:	4,250,000
Colour Index:	0.82
Leucocytes:	7,400

Splenectomy was performed the same day.

Eight days after splenectomy the patient was much improved; the jaundice had vanished. The blood findings were:-

Cholesterol in plasma:	0.067 %
Erythrocytes:	5,000,000.
Colour Index:	0.85
Leucocytes:	10,900.
Haemoglobin	85%.

Subsequent cholesterol determination was:-

15 days after operation:	0.087 %
21 " "	0.097 %

Case 10. is a case of Spenic Anaemia.

CASE X.

S.P. male, aged 37, was admitted to Hospital on 28th. September 1921 on account of recurrent attacks of haematemesis since 22nd. March 1921.

Has had no previous illness, there was no history of indigestion.

On admission patient looked pale, the pulse was rapid and of small amplitude, 110 per minute. The abdomen was full, and the spleen was much enlarged, extending half an inch below the level of the umbilicus.

On the 29th. October the blood findings were:-

Cholesterol in plasma: 0.123 %
Erythrocytes: 3,700,000:
Haemoglobin: 45%
Colour Index: 0.67
Leucocytes: 11,700

On 16th. November half pint of blood was transfused, patient's father being the donor.

Two days later splenectomy was performed. Nine days after the operation the blood findings were:-

Cholesterol in plasma: 0.113 %
" " corpuscles: 0.097 %

Nine days after operation the blood findings were:

Cholesterol in plasma: 0.142
Erythrocytes: 4,200.000
Haemoglobin: 45.
Colour Index: 0.6
Leucocytes: 7,300.

He was discharged on 17th. December much improved. He was seen again in the out patients' department 39 days after operation, when the blood findings were:-

Cholesterol in plasma: 0.181 %

59 days after operation the blood findings were:-

Cholesterol in plasma: 0.160 %

86 days after operation the blood findings were:-

Cholesterol in plasma: 0.200 %
" " carpuscles: 0.108 %

CASE XI. POSTAL CIRRHOSIS.

W.M. male, aged 14, was admitted to hospital on 30th. December 1920 complaining of a sensation of fulness in the abdomen of six weeks' duration. The patient had scarlet fever at the age of 7: at the age of 9 a radical mastoid operation was performed and he has been blind since.

The present illness began suddenly six weeks before admission with headache, and abdominal swelling which has increased in size since.

On admission the abdomen was full. The superficial veins were markedly distended, and there was a caput Medusae. There was marked ascites, the liver and spleen were enlarged. The Warsermann reaction was negative. Ophthalmoscopic examination revealed the presence of bilaterial optic atrophy. There was no fever.

On 2nd. February the blood findings were:-

Cholesterol in plasma:	0.087 per cent.
" " corpuscles:	0.107 " "
Erythrocytes:	6,200,000
Haemoglobin:	85.
Colour Index:	0.7
Leucocytes:	10,200.

The red cells appeared normal: no nucleated reds were seen.

A splenectomy was performed, andthe following day. The patient died three days later.

Numbers 12 and 13 are cases of Polycythaemia. Vera.

CASE XII.

R.R. male, aged 55. was admitted to Hospital 4th. February 1922, complaining of pain in the left side of the abdomen, and general weakness of 15 months duration.

He has always had a good deal of colour. On admission he was seen to be a well developed man,but thin. He was

tremendously cyanosed; the venules of the face were markedly distended. The spleen was much enlarged - extending well beyond the middle line anteriorly, and 5½ inches below the costal margin. There was tenderness over the spleen. The liver was also enlarged, extending 3½" below the costal margin. The cardiac and respiratory systems were normal.

On 6th. February the blood findings were:

Cholesterol in plasma:		0.074 %
"	" corpuscles	0.121 %
Erythrocytes:		9,500,000
Haemoglobin:		115 %
Colour Index:		0.67
Leucocytes:		21,200
Polymosphs:	Neutrophil	84.6
	Eosinophil	2.4
	Basophil	1.0
Large mononuclears:		2.4
Lymphocytes:		9.6

No nucleated red cells were seen. The blood volume (vital red method) was 4,800 c.c. i.e. 1.4 times the normal value, taking the normal value as 50 c.c. per Kilo of body weight. (Patient weighed 11 stones) The fragility of the red cells was increased.

On 22nd. February 400 c.c. of blood were removed by venesection.

The cholesterol content of the blood and the blood count were practically unchanged.

On 23rd. February 600 c.c. of blood were transfused to

a case of acholuric family jaundice.

On 7th. March the cholesterol contents of the blood plasma was found unchanged: 0.076 per cent.

Patient felt much better after the two bleedings. The colour was less florid, the spleen became reduced in size. He was discharged on 11th. March.

CASE XII.

M.H. female, aged 30, attended the Out Patient Department on account of extreme weakness of elevan months duration.

Patient was very cyanosed: the spleen was considerably enlarged.

On 12th. April 1922, the blood findings were:

Cholesterol in plasma:	0.190 %
" " corpuscles:	0.140 %
Erythrocytes:	7,700,000
Haemoglobin:	115 %
Colour Index:	0.75
Leucocytes:	9,800.

No nucleated reds were seen.

The fragility of the red cells was not determined.

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